SYNTHESIS OF SOME PHENYL- AND PYRIMIDINYL-PURINES AND RELATED PTERIDINES AS PHLEOMYCIN AMPLIFIERS

A Thesis

Submitted to

The Australian National University

for the Degree of

Doctor of Philosophy

by

KENYA MORI

Medical Chemistry Group

The John Curtin School of Medical Research

The Australian National University

Canberra

December, 1984

CERTIFICATE OF ORIGINALITY

The work described in this thesis was carried out by the candidate at The Australian National University. Where the work of others was employed or quoted, appropriate references have been included.

Kenya mori

ACKNOWLEDGEMENTS

The author wishes to express his gratitude to Dr D. J. Brown for his advice and encouragement on this project and on attitudes to research in general. Thanks also go to Drs W. L. F. Armarego, G. B. Barlin, W. B. Cowden, M. D. Fenn for helpful discussions, and to all members of the Medical Chemistry Group for help and support. I also thank Dr H. Taguchi for wise council to me during his Visiting Fellowship here. Mrs Rosemary Enge kindly typed this thesis. Thanks are also offered to The Australian National University for the award of a research scholarship and to Professor F. Yoneda for his encouragement from afar.

SUMMARY

Synthetic routes are described to 5,6-diamino-2,4'-bipyrimidin-4-ones and 4,5,6-triamino-2,4'-bipyrimidines, as key intermediates from the corresponding pyrimidine-4-carboxamidinium chlorides, and their subsequent conversions into 2-(pyrimidin-4'-yl)purines, 2-(pyrimidin-4'-yl)pteridines, 2-(pyrimidin-4'-yl)quinazolines, and 5-(pyrimidin-4'-yl)-(1H)-v-triazolo[4,5-d]pyrimidin-7(6H)-ones, some of which bear a sulfur- or nitrogen-linked basic side chain.

Synthetic routes are also described to a series of 2-, 6- and 8-phenylpurines, in which one hetero-ring has been replaced by an homocyclic system, each having an appropriate S- or NH-linked side chain elsewhere in the molecule; to 2- and 4-phenylpteridines, each with a similar side chain and some with two additional C-methyl groups; to 2- and 4-phenylquinazolines, each equipped with an analogous side chain; and to the 2-(pyridin-4'-yl)purine and 2-(pyridin-4'-yl)quinazoline analogues of the above.

The annelation of a (fused) imidazole ring to one pyrimidine ring of a 2,4'-bipyrimidine bearing a suitable side chain, had little effect on activities as amplifiers of phleomycin-G in an *in vitro* bacterial system; relocation of the basic side chain from the 6- to the 8-position in the resulting pyrimidinylpurines had a mildly deleterious effect.

The 2-phenylpurines, 2-phenylpteridines, and 2-phenylquinazolines with appropriate S- or NH-linked side chains are shown to have considerable activity, but isomers and methylthio analogues showed less activity while the 2-pyridin-4'-yl analogues could not be evaluated because of intrinsic antibacterial activity.

CONTENTS

CHAPTER I

INTRODUCTION

I-1 Phleomycin and Related Antibiotics

Phleomycin and related antibiotics[1-3] were isolated as Cu (II) complexes from the culture media of Streptomyces verticillus and proved to have wide-spectrum antimicrobial and some antitumor activity.[4-9] The copper in phleomycin can be removed by 8-hydroxyquinoline but this process does not affect the above activities.[10] The phleomycin molecule consists of four parts:

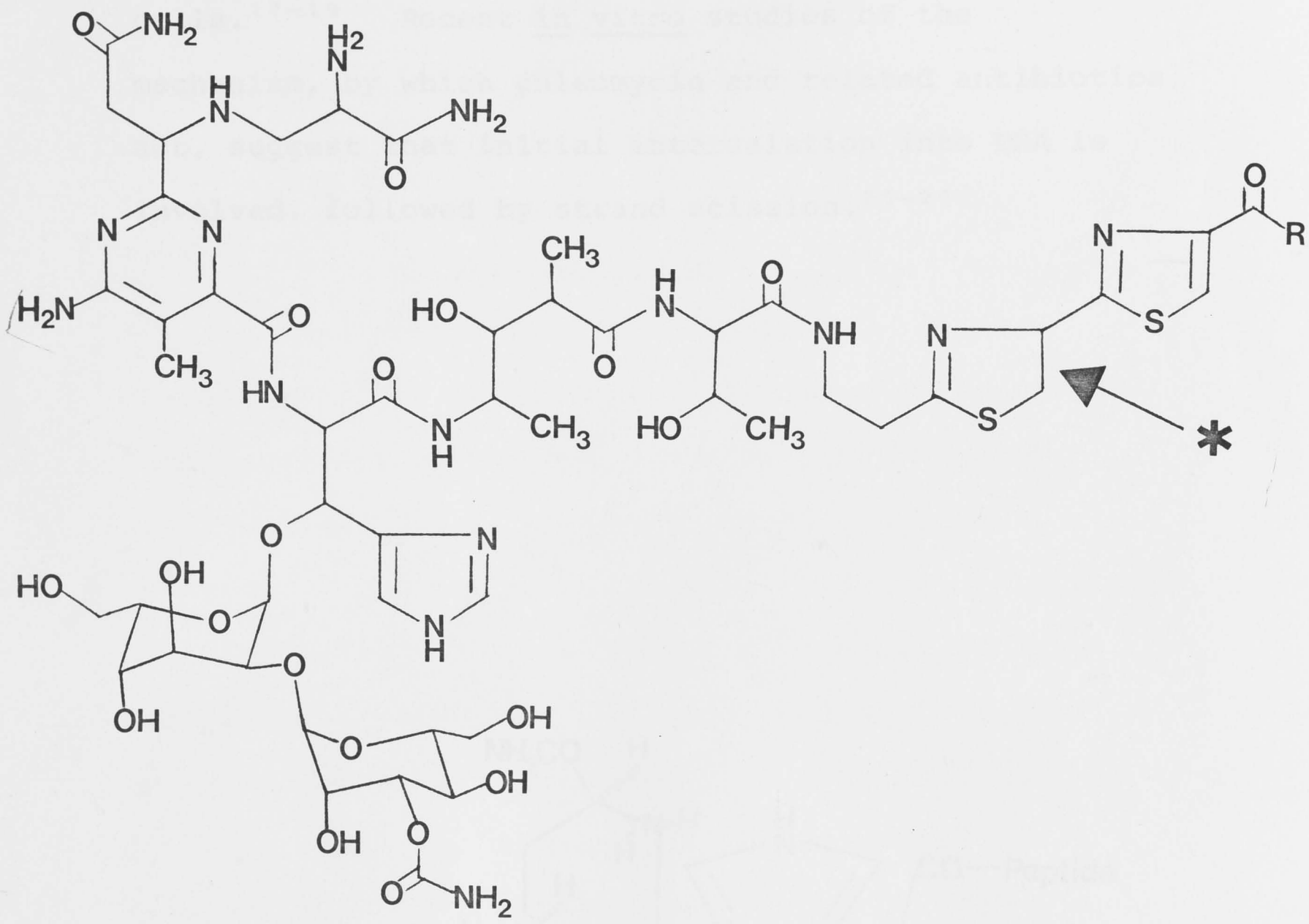
(i) a two-sugar portion;

(ii) a polypeptide portion containing a pyrimidine and imidazole ring;

(iii) a dihydrobithiazole portion; and

(iv) a polybasic side chain (see Fig. I-1).[2,11-13]

Related antibiotics[3,14] have closely similar structures. For example, bleomycins have a bithiazole instead of a dihydrobithiozole portion and phleomycins can therefore be converted by chemical oxidation with manganese dioxide into bleomycins.[2,11] The polybasic side chain varies somewhat in individual phleomycins according to the nutrient precursors available in the culture medium; also in bleomycins.[11,12] In 1978, the portion attached to the 2-position of the pyrimidine ring was revised: the supposed β-lactam ring turned out to be a pseudodipeptide, based on studies of the ^{13}C n.m.r. spectra.[15] The Cu (II)-complex of bleomycin (see Fig. I-2) is based firmly on X-ray crystallographic analysis.[16]



R = Terminal amine

Structure of phleomycins (as shown) and bleomycins (with an extra double bond at the starred position)

Fig. I-1

Phleomycins and related antibiotics inhibit selectively DNA synthesis in bacteria and in cancer cells.[17-19] Recent in vitro studies of the mechanism, by which phleomycin and related antibiotics act, suggest that initial intercalation into DNA is involved, followed by strand scission.[20-23]

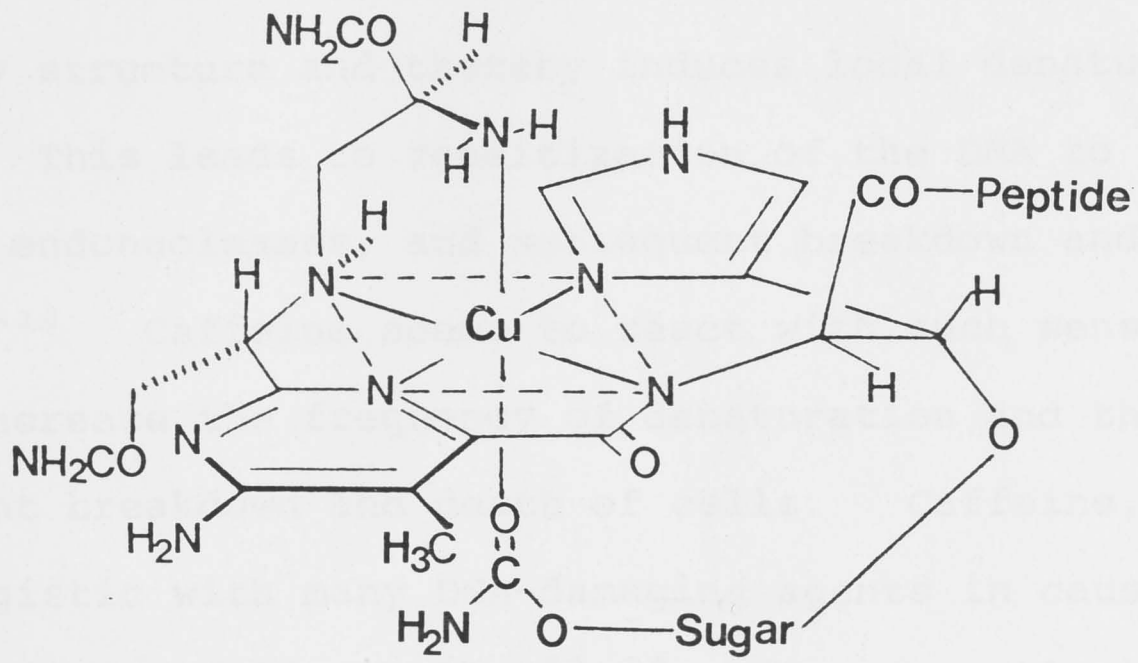


Fig. I-2

I-2 Amplification of Phleomycin

Indiction of DNA-breakdown and cell death occurs at low concentration (2 μg/ml) of phleomycin in growing Esherichia coli but not in cells at stationary phase: at higher concentration (≥10 μg/ml), death occurs at all stages.[24] In 1970, G. W. Grigg[25] observed that a high concentration of phleomycin had the same effect in E. coli as a combination of caffeine plus a lower concentration of phleomycin. Caffeine increased the lethal effects of the low concentration of phleomycin some 30-fold, but alone it had no effect on such a culture. The term "amplification" was adopted for this phenomenon.[25] It appears that phleomycin attaches itself to single-stranded DNA,[26,27] and thus distorts the secondary structure and thereby induces local denaturation in DNA. This leads to sensitization of the DNA to cellular endonucleases, and subsequent breakdown and death.[28-30] Caffeine seems to react with such sensitized DNA to increase the frequency of denaturation and the subsequent breakdown and death of cells. Caffeine, which is synergistic with many DNA-damaging agents in causing lethality in mammalian cells,[31,32] weakens normal hydrogen bonding of such denaturated regions of phleomycin-treated DNA. C. C. Lau et al.,[33] showed that caffeine potentiates the lethality of nitrogen-mustards by inducing damaged cells to undergo premature mitosis before repairing lesions in their DNA.

I-3 Potential Uses for Amplified Phleomycin

Phleomycin, like many antibiotic and other anti-cancer drugs, produces toxic side effects at therapeutically effective dosage levels.[7,34-37] The most troublesome side effects of phleomycin are its nephrotoxicity and lung toxicity. However, since the effective dose of phleomycin can be reduced considerably by using it in conjunction with caffeine, this offers a way to reduce or even eliminate such side effects. A great many potential amplifiers have been prepared and screened for amplifying activity on a bacterial system *in vitro* during the last decade.[38] In addition, it was hoped that the amplifier might be taken up specifically by cancer cells or by pathogens and hence confer an increased specificity on the corresponding phleomycin-amplifier regimes. In fact, some of the more active compounds in the screen have been tested as adjuvants of phleomycin against several types of tumor in rats and mice, with appreciable success.[39,40]

I-4 Amplifiers Unlike Caffeine

G. W. Grigg et al.,[29] observed that amplifying activity was shown by pyronine-Y, by a coumarin, and by a wide range of aromatic bi-, tri-, and tetra-cyclic hydrocarbons which are cationic or which can become positively charged by protonation at an attached nitrogen substituent.[41] The general structural requirements for such amplifiers are shown in Fig. I-3, but without the necessary substituents or heteroatom(s).

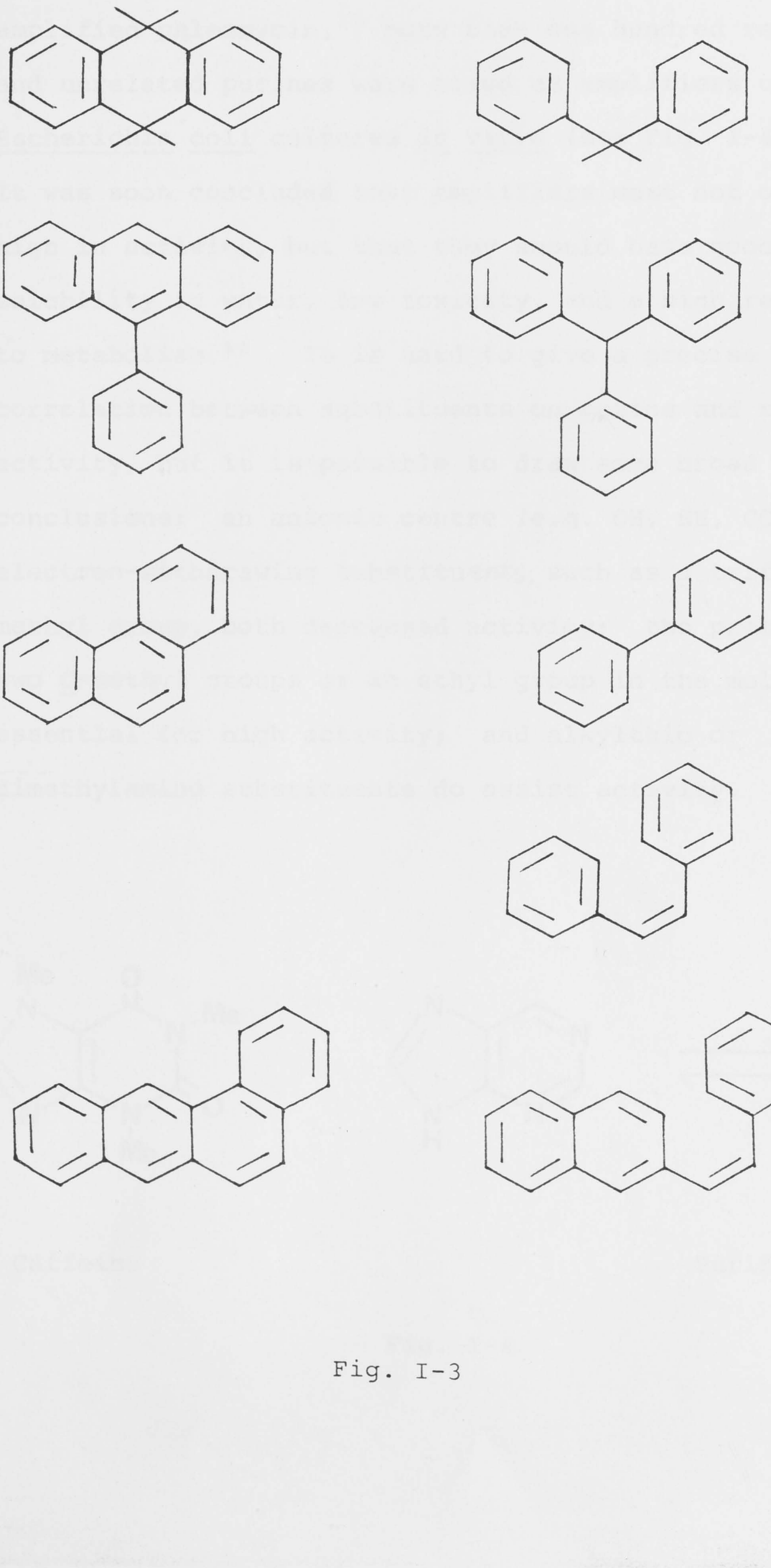
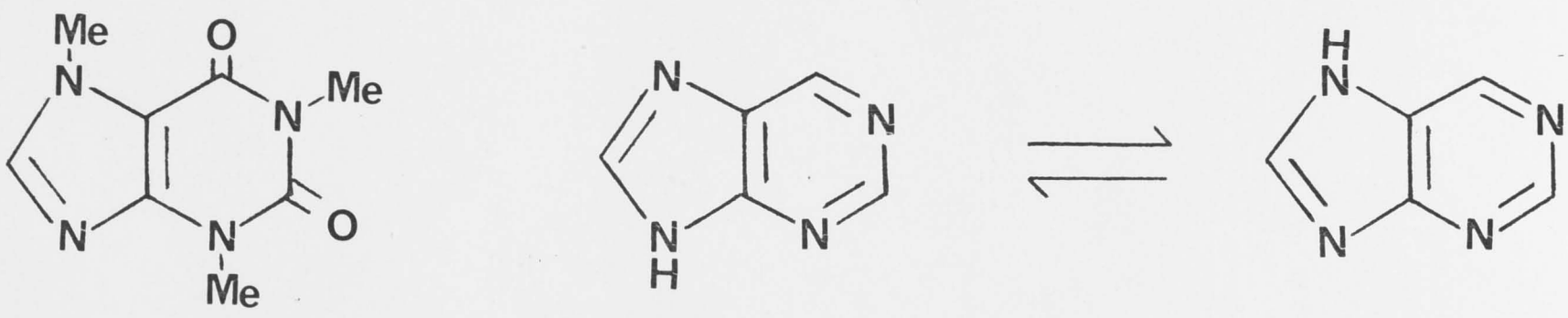


Fig. I-3

I-5 Fused Heterobicyclic Amplifiers

I-5 A. Purines

Following the original discovery that caffeine amplified phleomycin,[24] more than one hundred related and unrelated purines were tried as amplifiers using Escherichia coli cultures in vitro (see Fig. I-4).[29] It was soon concluded that amplifiers must not only be high in activity, but that they should have good solubility in water, low toxicity, and a high resistance to metabolism.[38] It is hard to give a precise correlation between substituents on purine and resulting activity, but it is possible to draw some broad tentative conclusions: an anionic centre (e.g. OH, SH, CO_2H) and electron-withdrawing substituents, such as a triflouro-methyl group, both decreased activity; the presence of two C-methyl groups or an ethyl group in the molcule was essential for high activity; and alkylthio or dimethylamino substituents do assist activity.



Caffeine Purine

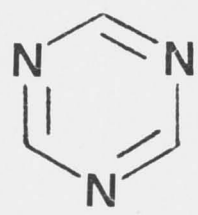
Fig. I-4

I-5 B. Heteromonocyclic Compounds and Their Benzo Derivatives

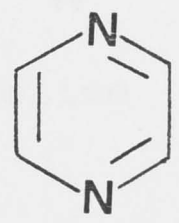
Pyrimidines, triazines, imidazoles, thiazoles, pyrazines and 1,2,4-triazoles, all with suitable substituents, were prepared and tested[42-44] in order to see whether a bicyclic or greater system was necessary for activity, or not (see Fig. I-5). Only a few such compounds showed any appreciable activity, and the five-membered heterocycles were almost lacking in activity.

Benzimidazoles, benzothiazoles, benzoxazoles, quinazolines, and quinolines, i.e. the above monocyclic systems fused with a benzene ring, exhibited much improved activities, but nearly all of those tried had very poor solubilities (see Fig. I-6)[43,45-48]

Pyrimidines

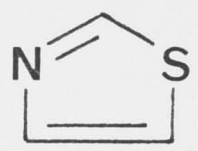


1,3,5-triazine

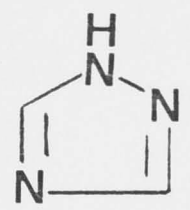


Pyrazine

imidazole

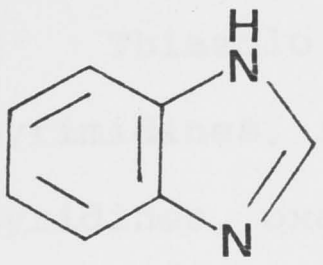


thiazole

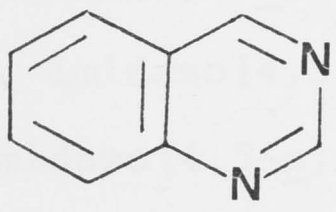


1,2,4-triazole

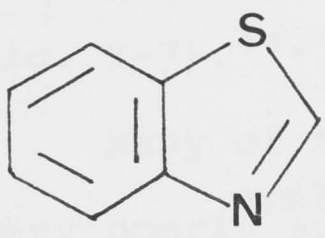
Fig. I-5



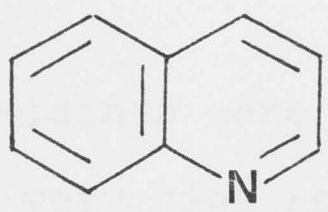
benzimidazole



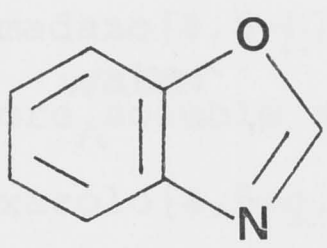
quinazoline



benzothiazole



quinoline



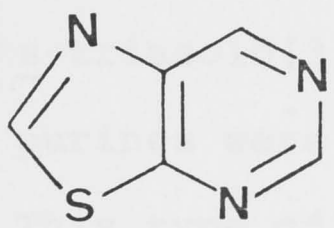
benzoxazole

Fig. I-6

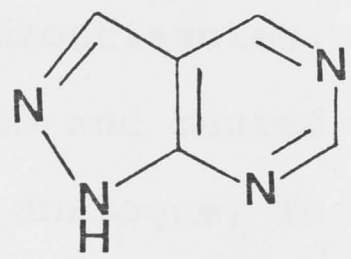
I-5 C. Heterobicyclic Purine Analogues

Thiazolo[5,4-d]pyrimidines, pyrazolo[3,4-d]-pyrimidines, imidazo[4,5-b]pyridines, imidazo[4,5-c]-pyridines, oxazolo[4,5-b]pyridine, imidazo[4,5-c]-pyridazines, imidazo[4,5-b]pyrazines, and thiazolo-[4,5-b]pyrazines were prepared and tested (see Fig. I-7).[42,44,46-48]

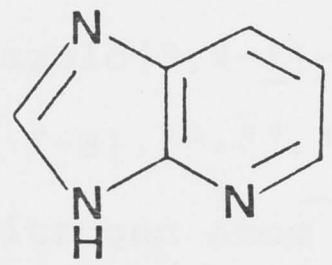
Many of the thiazolo[5,4-d]pyrimidines were very poorly water-soluble but a few showed very high activity. Only one of pyrazolo[3,4-d]pyridine showed good activity. Imadazo[4,5-b]pyridines and their [4,5-c] analogues were more water-soluble and showed quite high activities. Oxazolo[4,5-c]pyridazines and imidazo[4,5-b]pyrazines showed mediocre activity.



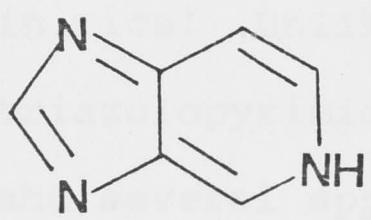
thiazolo[5,4-d]-
pyrimidine



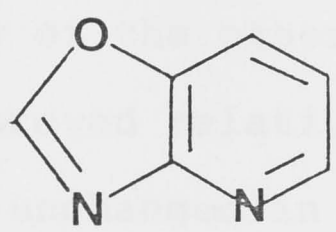
pyrazolo[3,4-d]-
pyrimidine



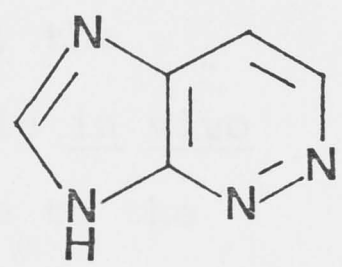
imidazo[4,5-b]-
pyridine



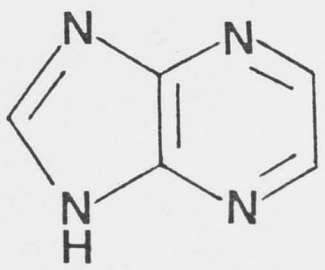
imidazo[4,5-c]-
pyridine



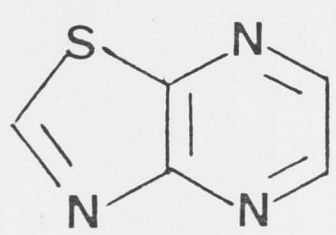
oxazolo[4,5-b]-
pyridine



imidazo[4,5-c]-
pyridazine



imidazo[4,5-b]-
pyrazine

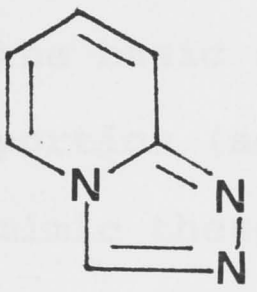


thiazolo[4,5-b]-
pyrazine

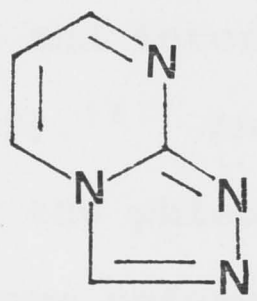
Fig. I-7

I-5 D. s-Triazolopyridines and Related Systems

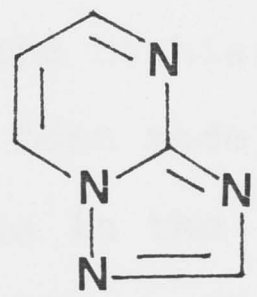
s-Triazolo[4,3-a]pyridines, s-triazolo[4,3-a]-pyrimidines, their Dimroth-rearranged [1,5-a] isomers, s-triazolo[4,3-c]pyrimidines, s-triazolo[1,5-c]pyrimidines s-triazolo[3,4-b]benzothiazoles, and s-triazolo[3,4-i]-purines were prepared and tested (see Fig. I-8).[42,45,49-52] This type of purine analogue, in which a nitrogen atom was shared between the five- and six-membered rings, reached very high activities with relatively good solubilities; in addition, they exhibited unusually low toxicities: one even showed on LD_{50} of >5000 mg/kg in mice! Unlike many of the other systems, the triazolopyrimidines proved relatively stable *in vivo* and several appeared unchanged in the urine to the extent of 50% or more. This is an obvious advantage for an amplifier.



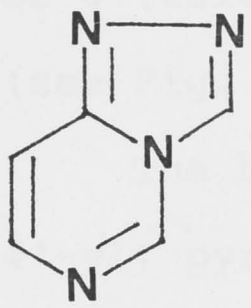
s-Triazolo[4,3-a]-
pyridine



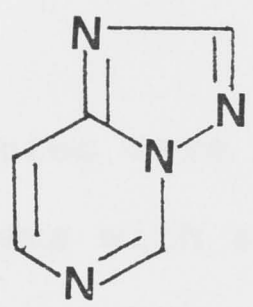
s-Triazolo[4,3-a]-
pyrimidine



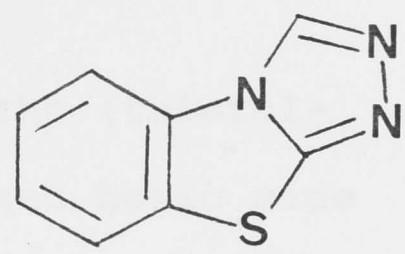
s-Triazolo[1,5-a]-
pyrimidine



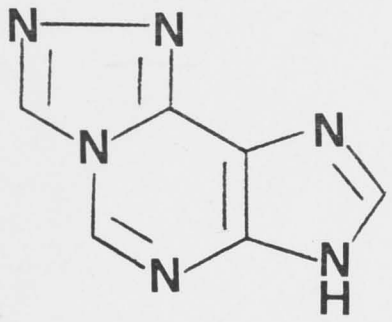
s-Triazolo[4,3-c]-
pyrimidine



s-Triazolo[1,5-c]-
pyrimidine



s-Triazolo[3,4-b]-
benzothiazoles



s-Triazolo[3,4-i]-
purines

Fig. I-8

I-6 Unfused Heterobicyclic Amplifiers

I-6 A. Thiazolylpyridines

The mechanism by which phleomycin and related antibiotics act, involves initial attachment to DNA by the basic side chain and intercalation of the bithiazole portion (see Fig. I-9).[16] An attempt has been made to mimic these parts of the phleomycin molecule in the molcular design of some unfused heterobicyclic amplifiers. Thus, 2-, 3- or 4-(thiazol-4'-yl)pyridines, and 2-, 3- or 4-(thiazol-2'-yl)pyridines were prepared and tested[53-55] (see Fig. 10).

The best activities were obtained in the (thiazol-4'-yl) pyridine systems with a sulphur-linked basic side chain. Whether such highly active unfused heterobicyclic amplifiers bind strongly to DNA has yet to be shown.

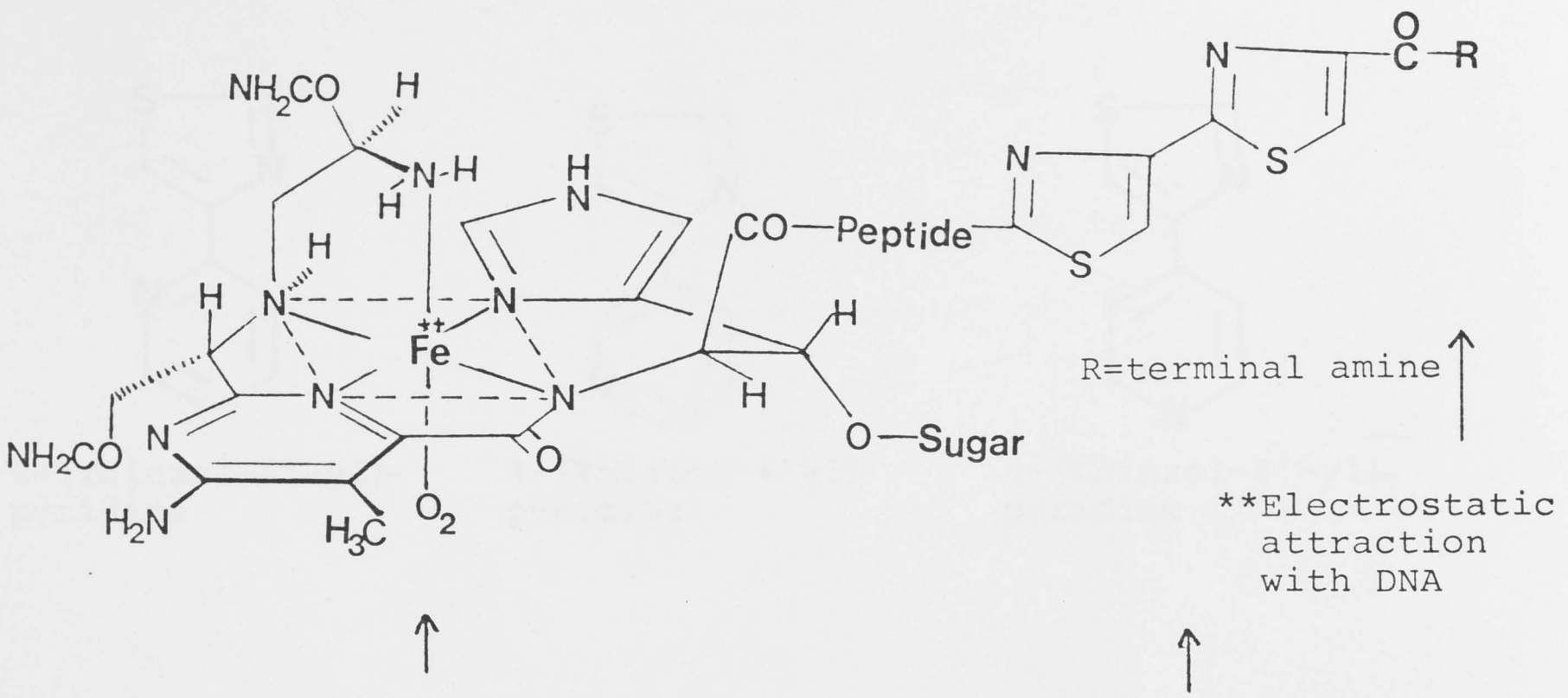
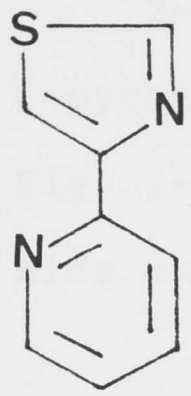
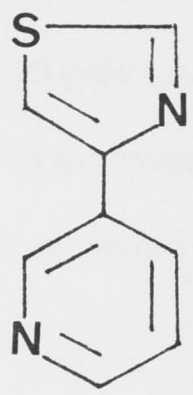

NH2CO
H
N-H
H
H
N
N
Fe
++
N
N
N
NH2CO
N
H2N
H3C
O2
O
H
N
CO—Peptide
N
S
S
O
C
R
H
O—Sugar
R=terminal amine
**Electrostatic attraction with DNA
Reaction with DNA
*Interaction with DNA

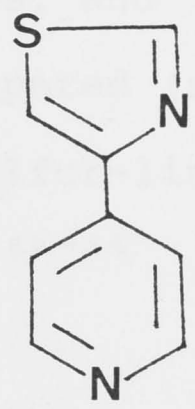
Fig. I-9



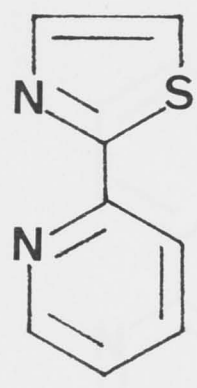
2-(Thiazol-4'-yl)-pyridine



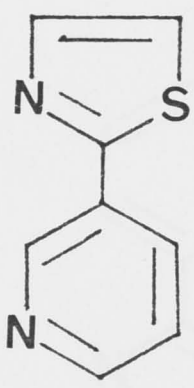
3-(Thiazol-4'yl)-pyridine



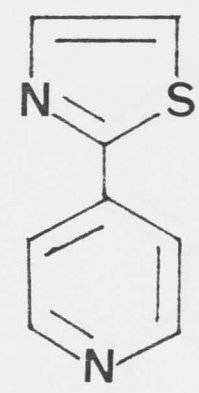
4-(Thiazol-4'-yl)-pyridine



2-(Thiazol-2'-yl)-pyridine



3-(Thiazol-2'-yl)-pyridine

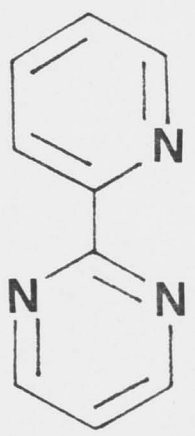


4-(Thiazol-2'-yl)-pyridine

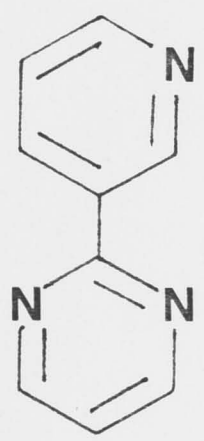
Fig. I-10

I-6 B. Pyridinyl- and Pyrazolyl — pyrimidines

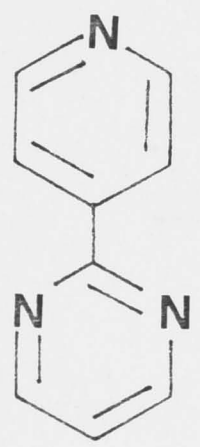
2-Pyridin-2', -3' or -4'-ylpyrimidines, and 4-pyrazol-1' or -4'-ylpyrimidines were prepared (see Fig. I-11) but only two compounds (with sulfur-linked side chains) reached a very high activity.[54-56]



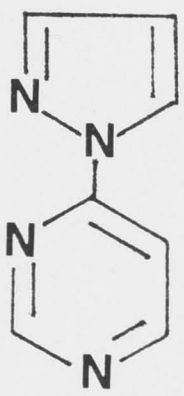
2-(Pyridin-2'-yl) pyrimidine



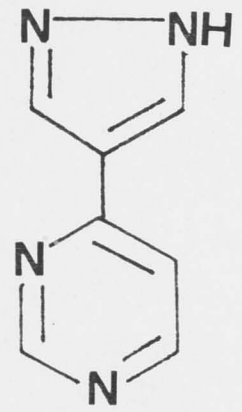
2-(Pyridin-3'-yl) pyrimidine



2-(Pyridin-4'-yl) pyrimidine



4-(Pyrazol-1'-yl) pyrimidine

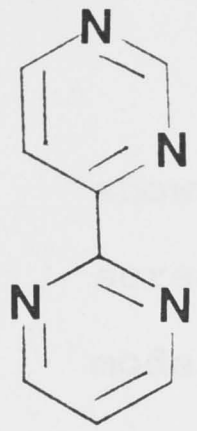


4-(Pyrazol-4'-yl) pyrimidine

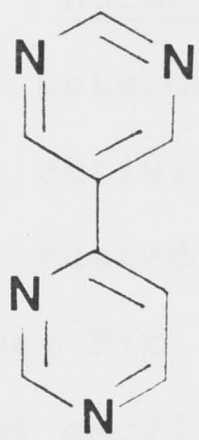
Fig. I-11

I-6 C. Bipyrimidines and Miscellaneous Systems

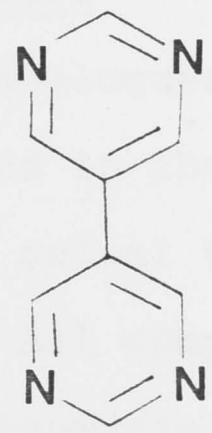
Derivatives of the three bipyrimidines, 4,5'-bithiazoles, 4-(thien-2'-yl)pyrimidines, 4-(thiazol-2'-yl)-pyrimidines, 2-(thiazol-4'-yl)pyrazines, and 4-phenylthiazole were prepared (see Fig. I-12).[53,54,56-58] Only one compound in each of the bipyrimidine systems, one 4-(thien-2-yl)pyrimidine, and a 4-phenylthiazole reached very high activities.



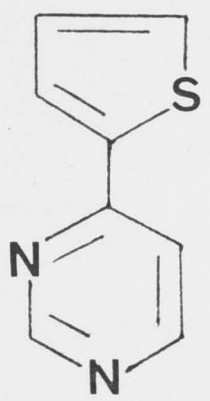
2,4'-Bipyrimidine



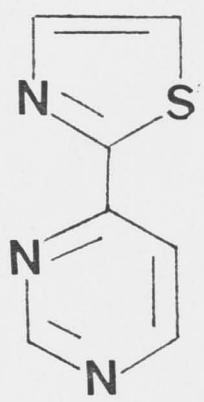
4,5'-Bipyrimidine



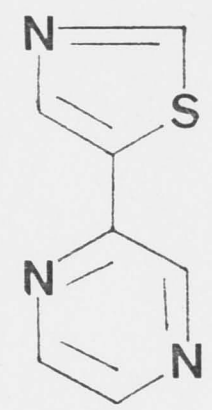
5,5'-Bipyrimidine



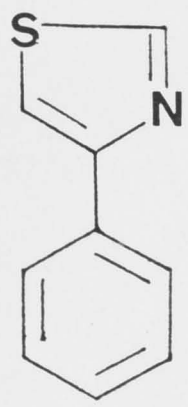
4-(Thien-2'-yl)-pyrimidine



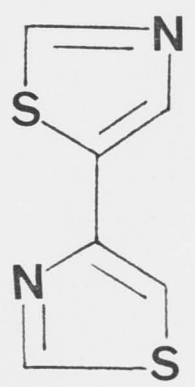
4-(Thiazol-2'-yl)-pyrimidine



2-(Thiazol-4'-yl)-pyrazine



4-Phenylthiazole

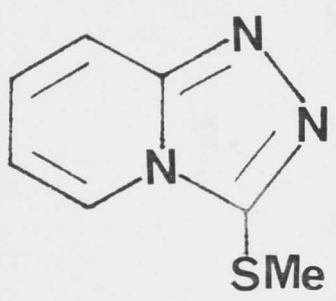


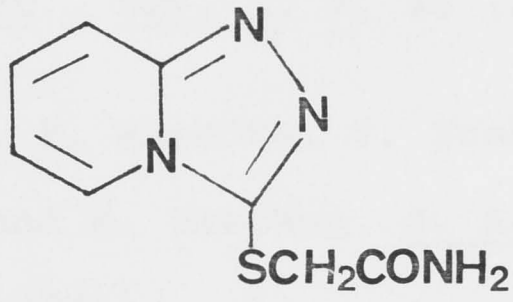
4,5'-Bithiazole

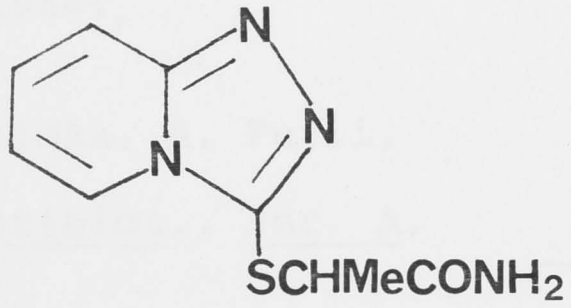
Fig. I-12

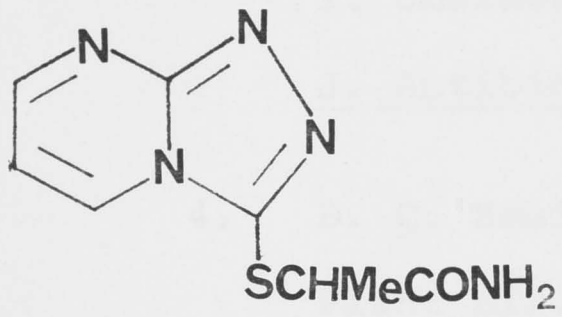
I-7 Antitumor Activity of Phleomycin plus Heterocyclic Amplifiers

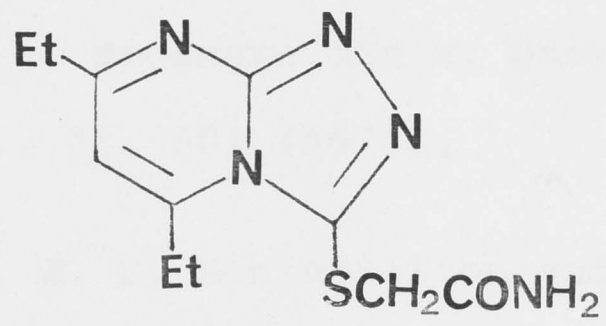
Eight of the heterocyclic purine analogues, which showed reasonable activity as amplifiers in the *in vitro* screen, have been tested against three animal tumor models in mice (see Fig. I-13).[39,40] All compounds showed significant amplification of phleomycin against at least one tumor type. The dose levels of both the phleomycin and amplifier proved very important and the optimal levels varied widely with actual agents used.

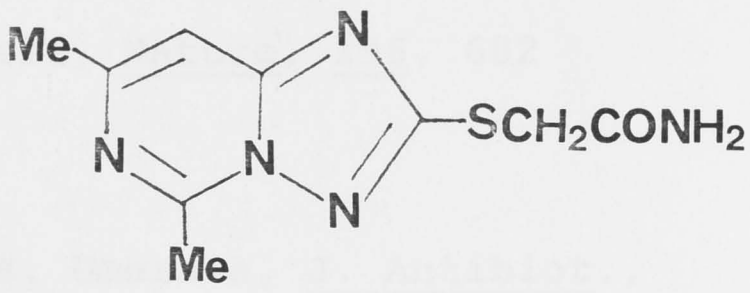

N
N
N
SMe

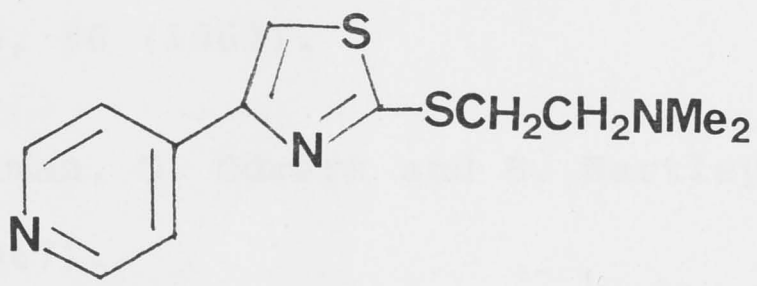

N
N
N
SCH2CONH2

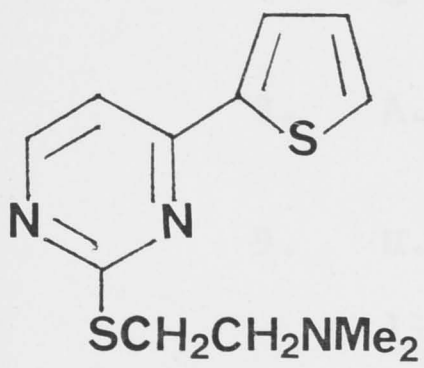

N
N
N
SCHMeCONH2


N
N
N
N
SCHMeCONH2


Et
N
N
N
N
Et
SCH2CONH2


Me
N
SCH2CONH2
N
N
N
Me


S
SCH2CH2NMe2
N
N


S
N
N
SCH2CH2NMe2

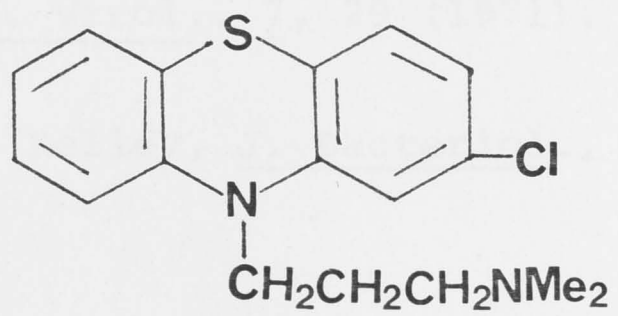

S
Cl
N
CH2CH2CH2NMe2

Fig. I-13

REFERENCES

1. K. Maeda, H. Kosaka, G. Yagishita and H. Umezawa, J. Antibiot., Ser. A, 9, 82 (1956).

2. T. Takita, Y. Muraoka, T. Yoshioka, A. Fujii, K. Maeda and H. Umezawa, J. Antibiot., Ser. A, 25, 755 (1972).

3. T. Takita, Y. Muraoka, T. Nakatani, A. Fujii, Y. Umezawa, N. Naganawa and H. Umezawa, J. Antibiot., 31, 801 (1978).

4. B. C. Smale, M. D. Montagillion and T. G. Pridham, Plant Dis. Rep., 45, 244 (1961).

5. W. T. Bradner and M. H. Pindell, Nature, 196, 682 (1962).

6. N. Tanaka, H. Yamaguchi and H. Umezawa, J. Antibiot., Ser. A, 16, 86 (1963).

7. B. A. Kihlman, G. Odmark and B. Hartley, Mutat. Res., 4, 783 (1967).

8. A. Iwata and R. A. Consigli, J. Virol., 7, 29 (1971).

9. H. Reiter, M. Milewskiy and P. Kelley, J. Bacteriol., 111, 586 (1972).

10. T. Takita, K. Maeda and H. Umezawa, J. Antibiot., Ser. A, 12, 111 (1959).

11. T. Takita, Y. Muraoka, A. Fujii, H. Itoh, K. Maeda and H. Umezawa, J. Antibiot., Ser. A, 25, 197 (1972).

12. A. Fujii, T. Takita, K. Maeda and H. Umezawa, J. Antibiot., Ser. A, 26, 398 (1973).

13. N. K. Hart, A. Hofman, J. A. Lamberton and M. N. Galbraith, Heterocycles, 13, 271 (1979).

14. M. Konishi, K. Saito, K. Numata, T. Tsuno, K. Asama, T. Tsukiura, T. Naito and H. Kawaguchi, J. Antibiot., 30, 789 (1977).

15. T. Takia, Y. Muraoka, T. Nakatani, A. Fujii, Y. Umezawa, H. Nagawa and H. Umezawa, J. Antibiot, 31, 801 (1978).

16. T. Takita, Y. Muraoka, T. Nakatani, A. Fujii, Y. Iitaka and H. Umezawa, J. Antibiot, 31, 1073 (1978).

17. N. Tanaka, H. Yamaguchi and H. Umezawa, Biochem. Biophys. Res. Comm, 10, 171 (1963), J. Antibiot., 16, 86, (1983).

18. A. Falasshi and A. Kornberg, Fed. Proc, 23, 940, (1964).

19. N. Tanaka, J. Antibiot., 18, 111 (1965).

20. H. Umezawa in Antiobiotics, Eds Corcoran and Hahn, Springer-Verlag, New York, 1975, vol. 3, p. 21.

21. P. Pietsch, Handb. Exp. Pharmakol., 38, 850 (1975)

22. A. P. Grollman and M. Takeshita, Adv. Enzyme Regul., 18, 67 (1980).

23. R. M. Burger, J. Peisach and S. B. Horwitz, Life Sci., 28, 715 (1981).

24. G. W. Grigg, Mol. Gen. Genet., 104, 1 (1969).

25. G. W. Grigg, Mol. Gen. Genet., 107, 162 (1970).

26. A. Falaschi and A. Kornberg, Fed. Proc., Fed. Am. Soc. Exp. Biol., 23, 940 (1964).

27. P. Pietsch and C. Corbett, Nature, 219, 933 (1968).

28. M. J. Sleigh and G. W. Grigg, FEBS Lett., 39, 35 (1974).

29. G. W. Grigg, M. J. Edwards and D. J. Brown, J. Bacteriol., 107, 599 (1971).

30. G. W. Grigg, J. Gen. Microbiol., 70 221 (1972).

31. B. A. Kihlman, Caffeine and Chromosomes, 1977, (Elsevier, Amsterdam).

32. J. Timson, Mutat. Res, 47, 1 (1977).

33. C. C. Lau and A. B. Pardee, Proc. Natl. Acad. Sci. USA 79, 2942, (1982).

34. E. Mattingly, Mutat. Res., 4, 51 (1967).

35. M. J. Sleigh and G. W. Grigg, Biochem. J., 155, 87 (1976); Mutat. Res., 42, 181 (1977).

36. N. Rakieten, M. V. Nadkarni, M. L. Rakieten and B. S. Gordon, Toxicol. Appl. Pharmacol., 14, 590 (1969).

37. M. Ishizuka, H. Takayama, T. Takeuchi and H. Umezawa, J. Antibiot., Ser. A, 19, 260 (1966).

38. D. J. Brown and G. W. Grigg, Med. Res. Rev., 2, 193 (1982).

39. T. E. Allen, D. J. Brown, W. B. Cowden, G. W. Grigg, N. K. Hart, J. A. Lamberton and A. Lane, J. Antibiot., 37, 376 (1984).

40. A. N. Aliano, T. E. Allen, D. J. Brown, W. B. Cowden, G. W. Grigg, D. Kavulak, and S.-B. Lan, Aust. J. Chem., 37, 2385 (1984).

41. G. W. Grigg, A. M. Gero, J. M. Hughes, W. H. F. Sasse, M. Bleise, N. K. Hart, O. Johansen, and P. Kissane, J. Antibiot., 30, 870 (1977).

42. D. J. Brown, G. W. Grigg, Y. Iwai, K. N. McAndrew, T. Nagamatsu and R. van Heeswyck, Aust. J. Chem., 32, 2713 (1979).

43. D. J. Brown, W. C. Dunlap, G. W. Grigg and L. Danchwerts, Aust. J. Chem., 31, 447 (1978).

44. G. B. Barlin, Aust. J. Chem., 36, 983 (1983).

45. D. J. Brown and Y. Iwai, Aust. J. Chem., 32, 2727 (1979).

46. D. J. Brown, W. C. Dunlap, G. W. Grigg and J. Kelly, Aust. J. Chem., 30, 1775 (1977).

47. D. J. Brown, L. Danckwerts, G. W. Grigg and Y. Iwai, Aust. J. Chem., 32, 453 (1979).

48. G. B. Barlin, Aust. J. Chem., 35, 2299 (1982).

49. D. J. Brown, W. C. Dunlap, G. W. Grigg, L. Danckwerts and T. Nagamatsu, Aust. J. Chem., 31, 397 (1978).

50. D. J. Brown and K. Shinozuka, Aust. J. Chem., 35, 1263 (1982).

51. D. J. Brown and K. Shinozuka, Aust. J. Chem., 34, 189 (1981); 34, 2635 (1981).

52. D. J. Brown and T. Nagamatsu, Aust. J. Chem., 32, 1585 (1979); D. J. Brown and K. Shinozuka, Aust. J. Chem., 33, 1147 (1980).

53. D. J. Brown, W. B. Cowden and L. Strekowski, Aust. J. Chem., 34, 1353 (1981).

54. D. J. Brown, B. B. Buttler, W. B. Cowden, G. W. Grigg, D. Kavulak and D. M. Podger, Aust. J. Chem., 34, 2423 (1981).

55. D. J. Brown, W. B. Cowden, G. W. Grigg and D. Kavulak, Aust. J. Chem., 33, 2291 (1980).

56. A. Kowalewski, L. Strekowski, M. Szajda, K. Walenciak and D. J. Brown, Aust. J. Chem., 34, 2629 (1981).

57. G. B. Barlin, Aust. J. Chem., 37, 1049 (1984).

58 D. J. Brown, W. B. Cowden, and L. Strekowski, Aust. J. Chem., 35, 1209 (1982).

CHAPTER II

SYNTHESIS OF SOME 2-PYRIMIDINYL-HETEROBICYCLES

II-1 Introduction

Unfused heterobicyclic systems, such as the bipyrimidines, are known to enhance the activity of phleomycin as an antibacterial or antitumor[1-4] agent. However, heteromonocyclic compounds have little effect on activity[5] although systems in which such heterocycles are fused with a benzene ring (to give fused heterocyclic systems such as quinazoline) do show considerable activity.[6] To date, heterocyclic systems, in which one pyrimidine ring of a bipyrimidine is fused with a second heterocyclic ring, have not been prepared and tested as amplifiers of phleomycin. Hence a series of pyrimidinyl-heterobicycles have now been prepared to represent such potential amplifiers.

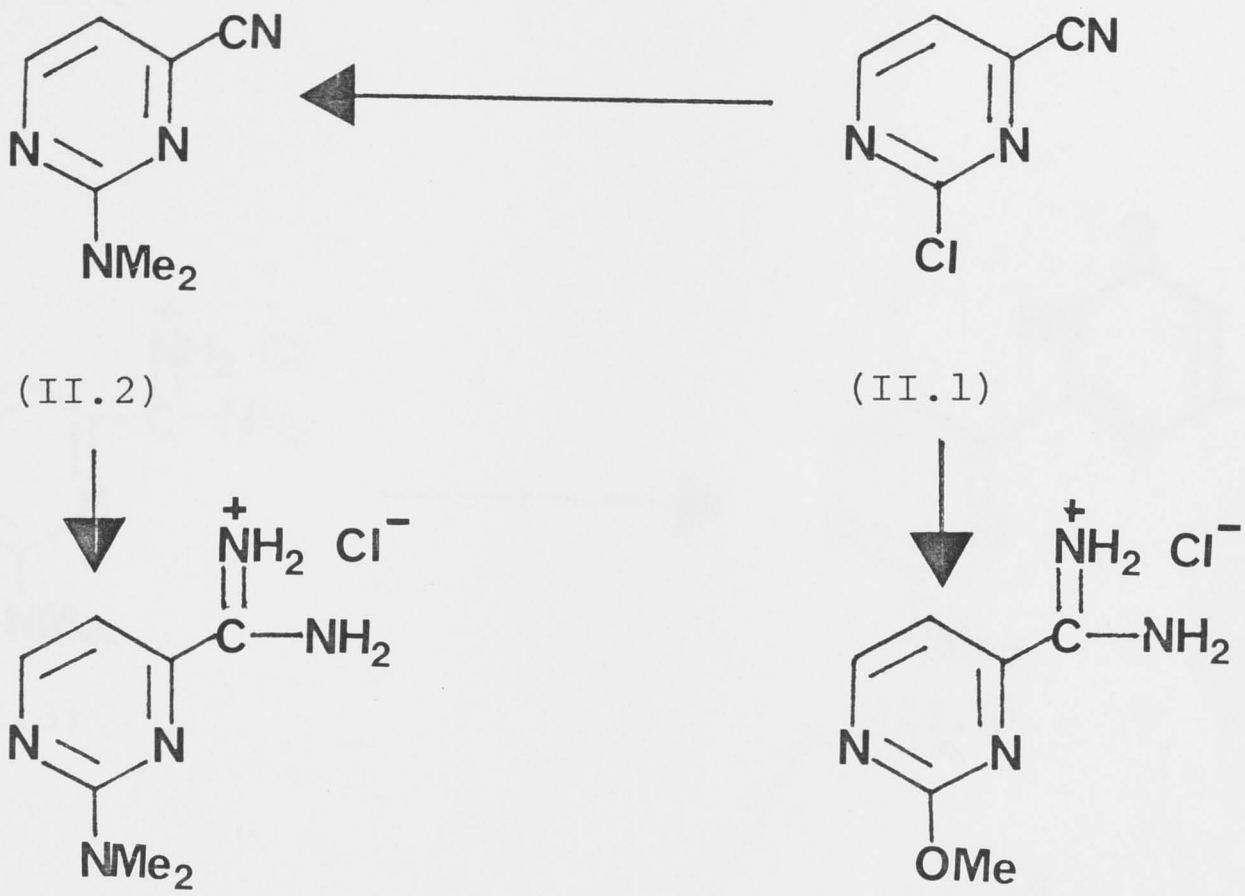
II-2 Preparation of 2,4'-Bipyrimidines

Treatment of 2-dimethylaminopyrimidine-4-carbonitrile[7] (II.2), which was prepared from 2-chloropyrimidine-4-carbonitrile[8] (II.1) by a known method, with methanolic sodium methoxide and ammonium chloride conveniently gave the amidinium chloride (II.3). Likewise, 2-chloropyrimidine-4-carbonitrile[8] (II.1) was converted, by successive treatment with methanolic sodium methoxide and ammonium chloride, into the analogous amidinium chloride (II.4) (Scheme II-1).

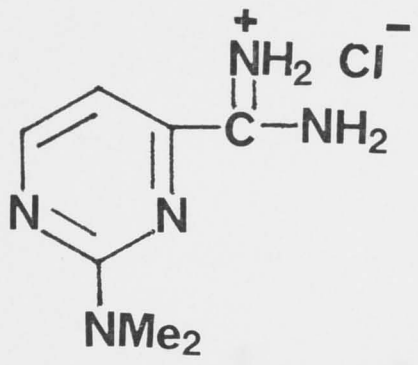
Condensation of the above 2-dimethylaminopyrimidine-4-carboxamidinium chloride (II.3) with ethyl cyanoacetate in ethanolic sodium ethoxide gave a separable mixture of the bipyrimidine (II.5) and the pyrimidinylacrylate (II.6) (Scheme II-2).

Nitrososation of the bipyrimidine (II.5) gave the 5-nitrosobipyrimidine (II.7), but it proved more effective to make the nitroso derivative (II.7) directly, and without any by-product, by condensing the amidine (II.3) with ethyl 2-cyano-2-hydroxyiminoacetate.[9] In much the same way, the amidine (II.4) gave the nitroso derivative (II.8) and the condensation of α-hydroxyiminomalononitrile[10] with the amidines (II.3,4) gave the nitroso derivatives (II.9,10) (Scheme II-3).

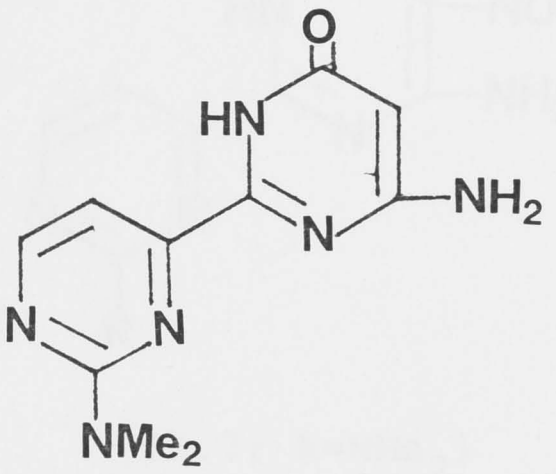
Dithionite reduction of the nitroso compounds (II.7,8) gave the diaminobipyrimidinones (II.11,12); the other nitroso compounds (II.9,10) gave the triaminobipyrimidines (II.13,14) (Scheme II-4).


CN
N
N
NMe2
(II.2)
CN
N
N
Cl
(II.1)
+
NH2 Cl−
C—NH2
N
N
NMe2
(II.3)
+
NH2 Cl−
C—NH2
N
N
OMe
(II.4)

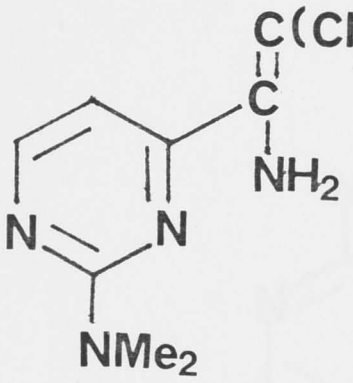
Scheme II-1



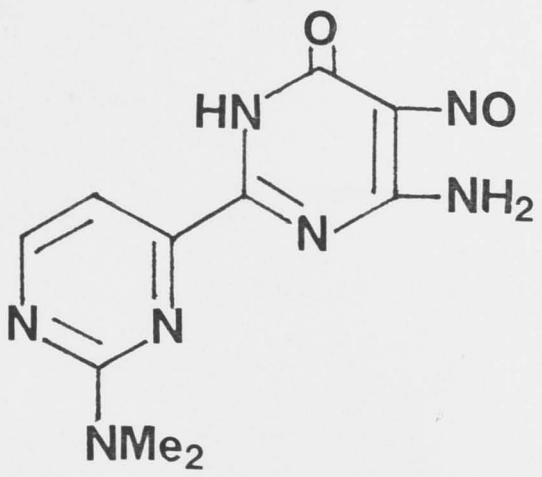
(II.3)



(II.5)

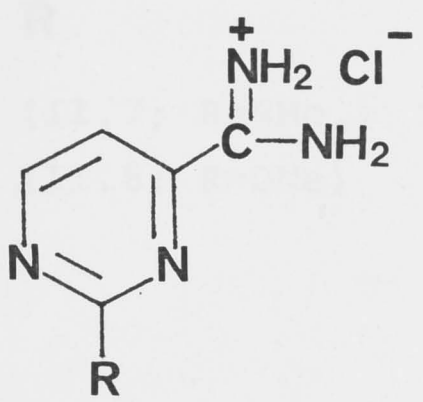


(II.6)

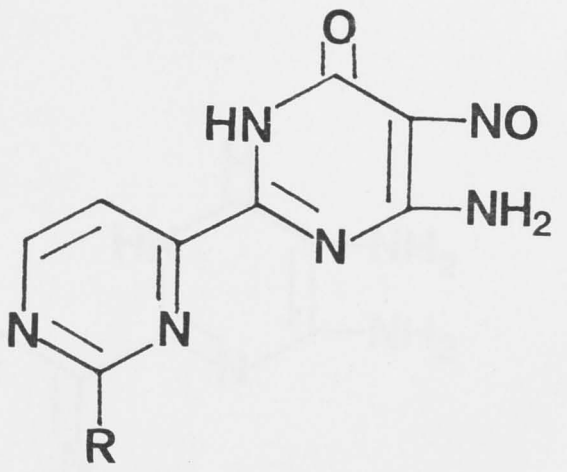


(II.7)

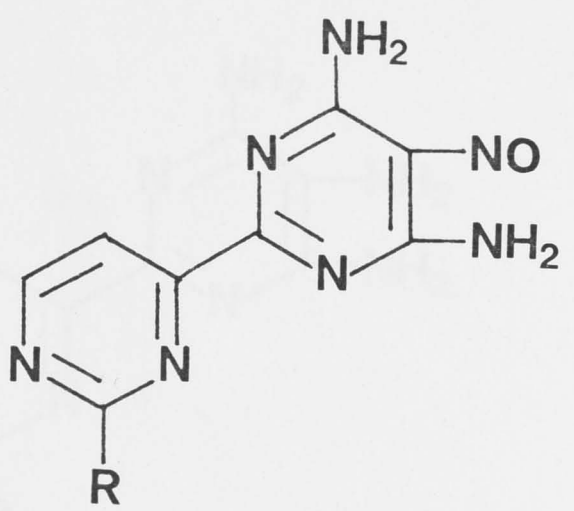
Scheme II-2



(II.3; R=NMe_2)
(II.4; R=OMe)

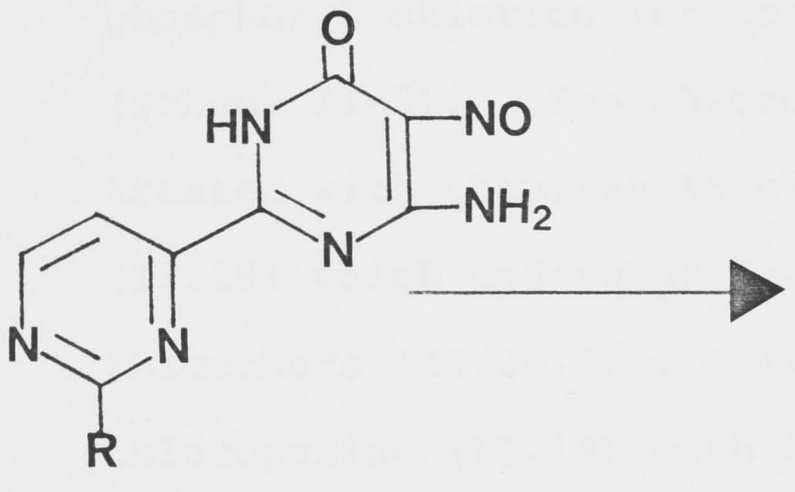


(II.7; R=NMe_2)
(II.8; R=OMe)

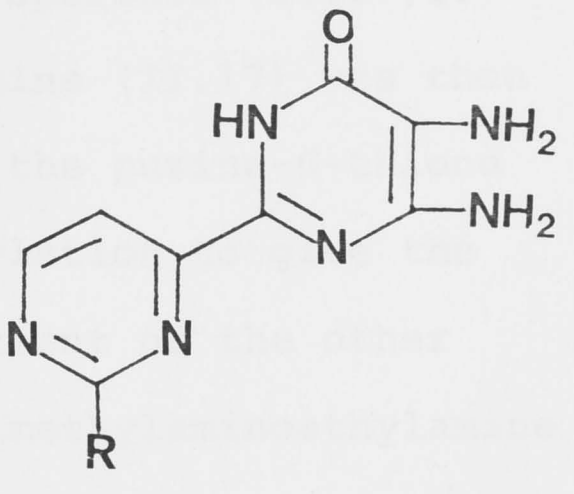


(II.9; R=NMe_2)
(II.10; R=OMe)

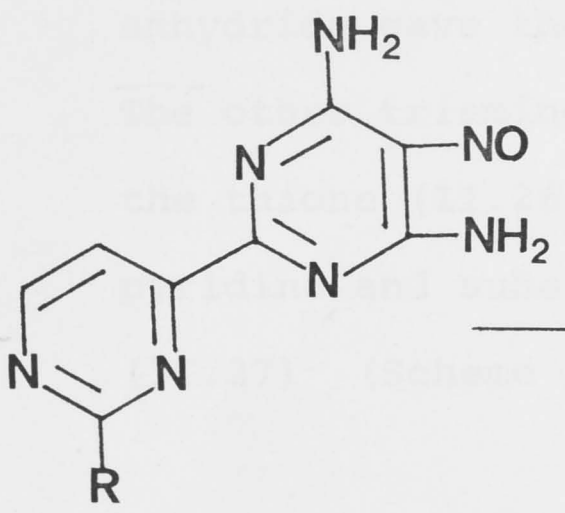
Scheme II-3



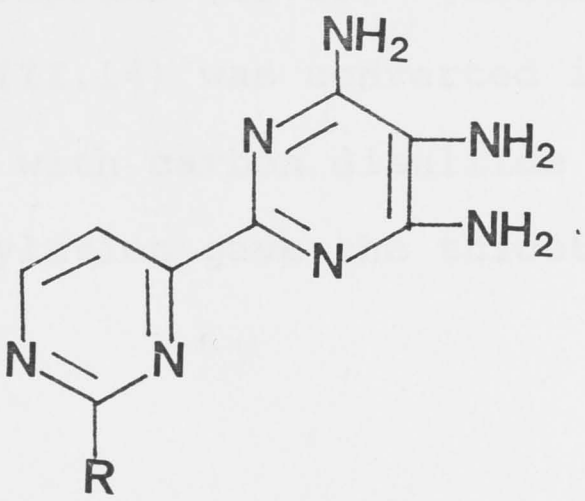
(II.7; R=NMe_2)
(II.8; R=OMe)



(II.11; R=NMe_2)
(II.12; R=OMe)



(II.9; R=NMe_2)
(II.10; R=OMe)



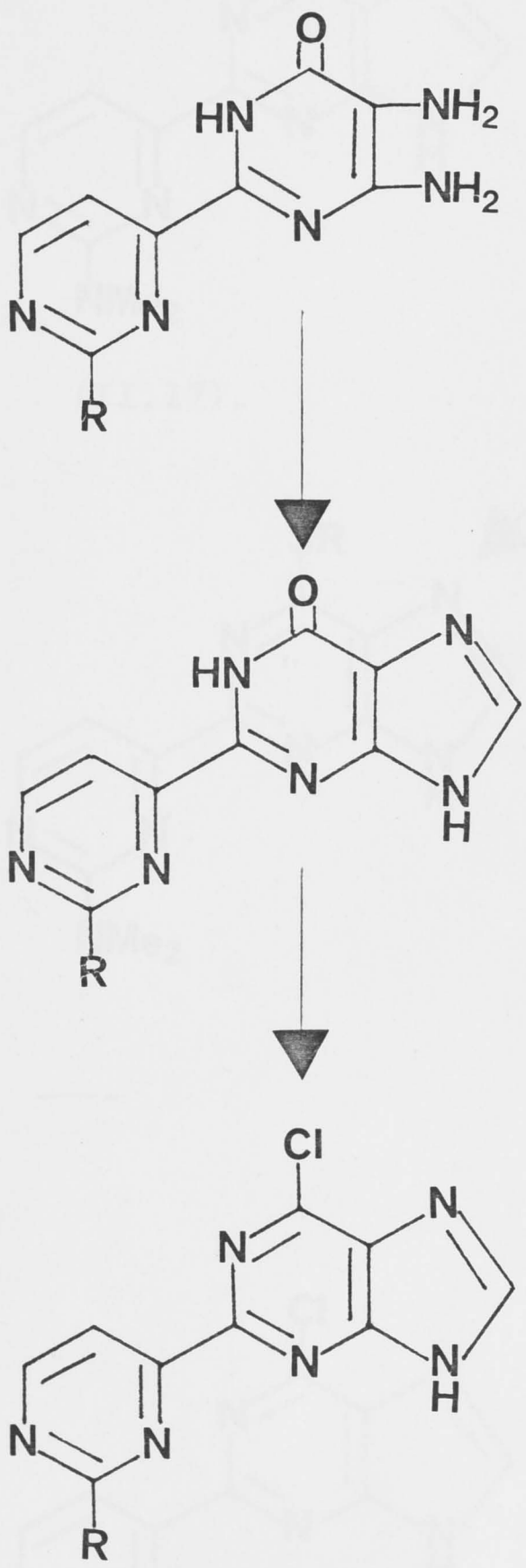
(II.13; R=NMe_2)
(II.14; R=OMe)

Scheme II-4

II-3 Preparation of 2-(Pyrimidin-4'-yl)purines

The diaminobipyrimidinones (II.11,12) reacted with triethyl orthoformate in acetic anhydride to give the purin-6-ones (II.15,16). These were converted by phosphoryl chloride into the chloropurines (II.17,18) (Scheme II-5). The chloropurine (II.17) was then treated with thiourea to give the purine-6-thione (II.19) which underwent S-alkylation to give the thioethers (II.20,21). Treatment of the other chloropurine (II.18) with 2-dimethylaminoethylamine gave the dimethylaminoethylaminopurine (II.22) (Scheme II-6).

Fusion of the triaminopyrimidine (II.13) with thiourea at 220° gave the purine-8-thione (II.23) which underwent S-alkylation to give the thioether (II.24). Acetylation of the thioether (II.24) with acetic anhydride gave the diacetyl compound (II.25) (Scheme II-7). The other triaminopyrimidine (II.14) was converted into the thione (II.26) by boiling with carbon disulfide in pyridine and subsequent S-alkylation gave the thioether (II.27) (Scheme II-8).

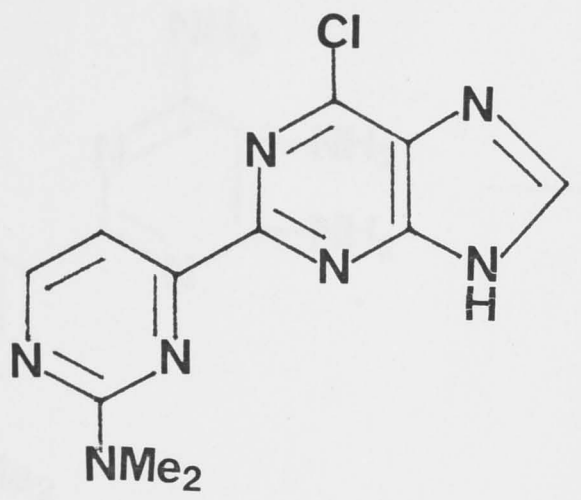


(II.11; R=NMe_2)
(II.12; R=OMe)

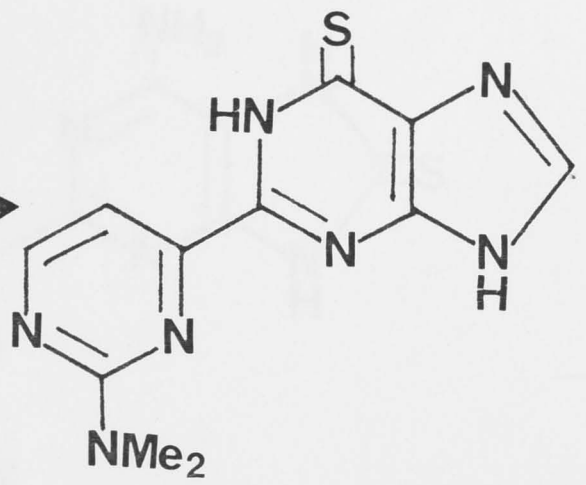
(II.15; R=NMe_2)
(II.16; R=OMe)

(II.17; R=NMe_2)
(II.18; R=OMe)

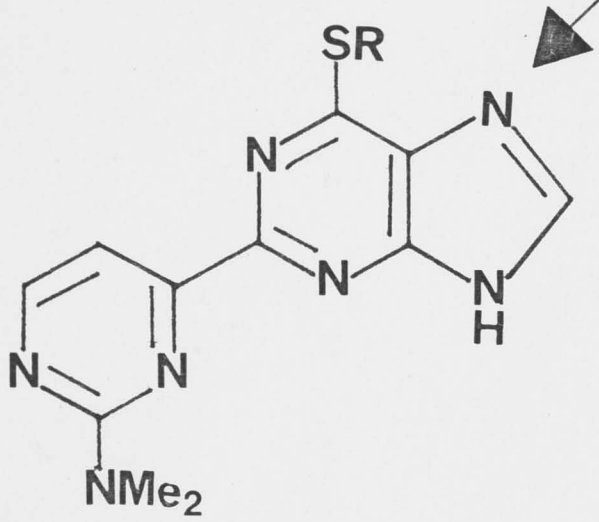
Scheme II-5



(II.17)

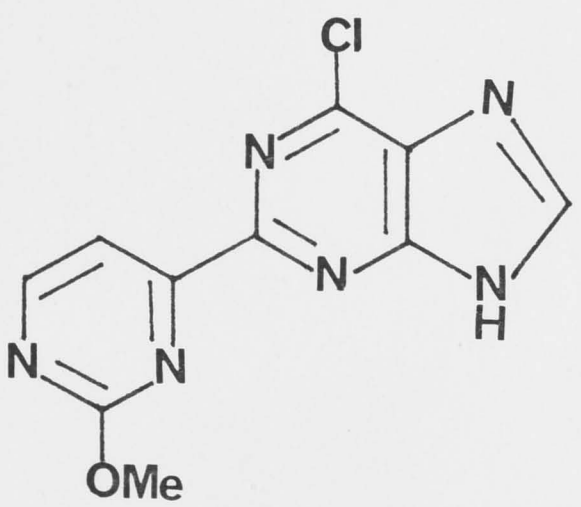


(II.19)

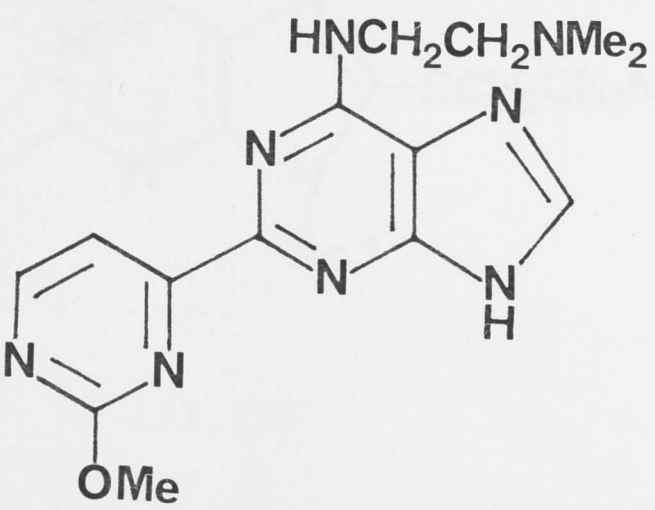


(II.20; R=Me)

(II.21; R= $CH_2CH_2NMe_2$)

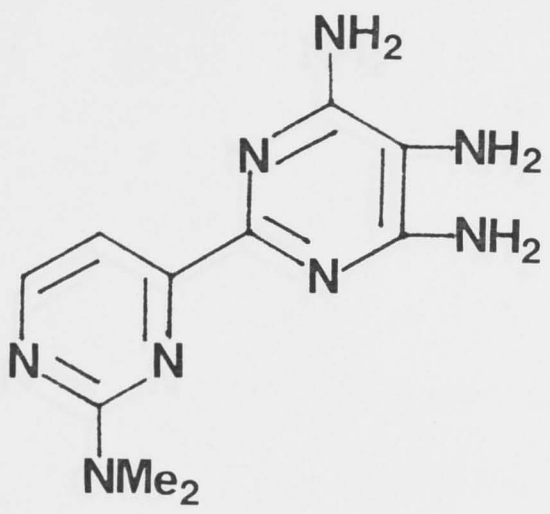


(II.18)

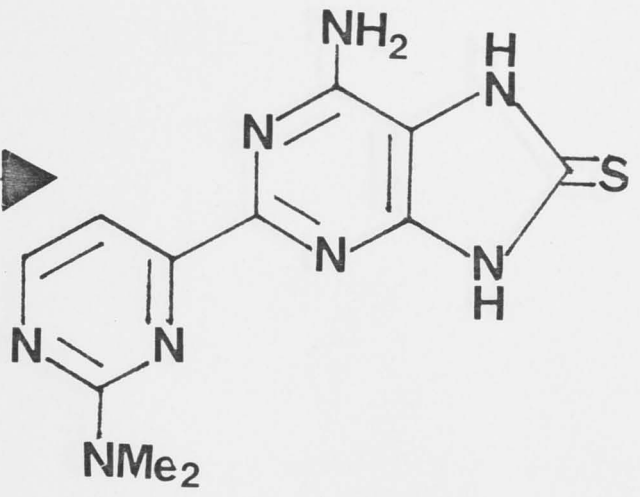


(II.22)

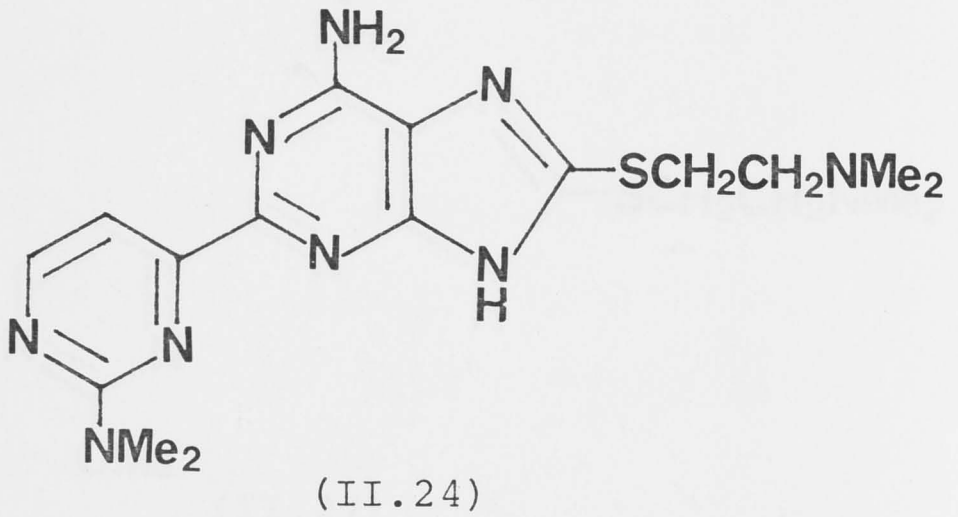
Scheme II-6



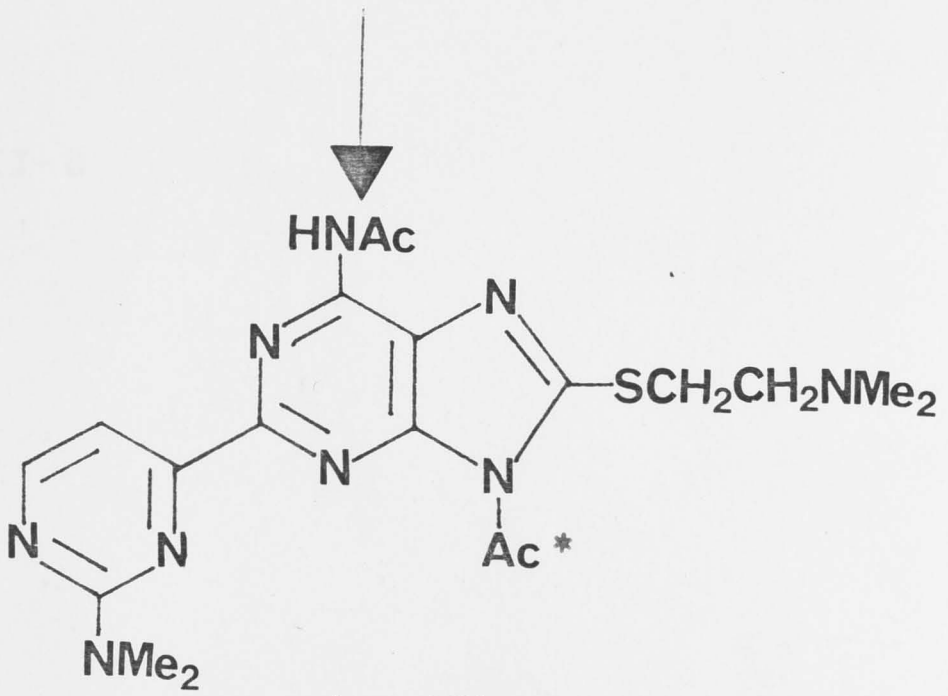
(II.13)



(II.23)



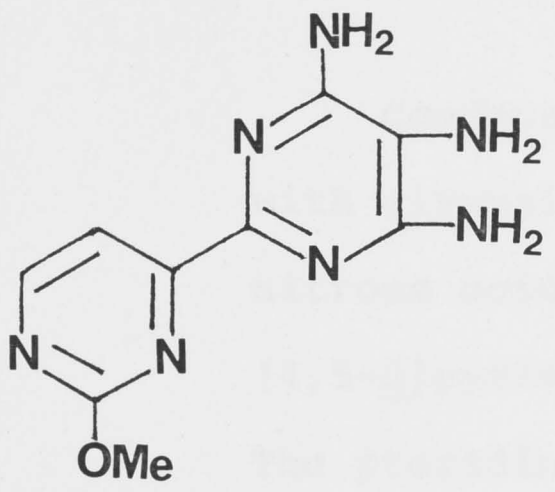
(II.24)



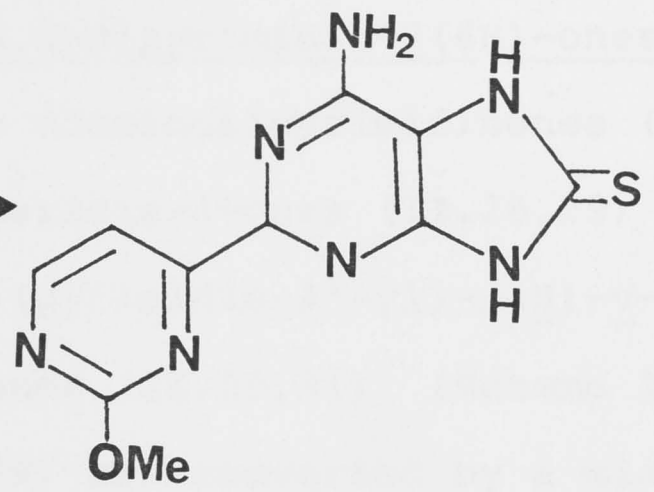
(II.25)

Scheme II-7

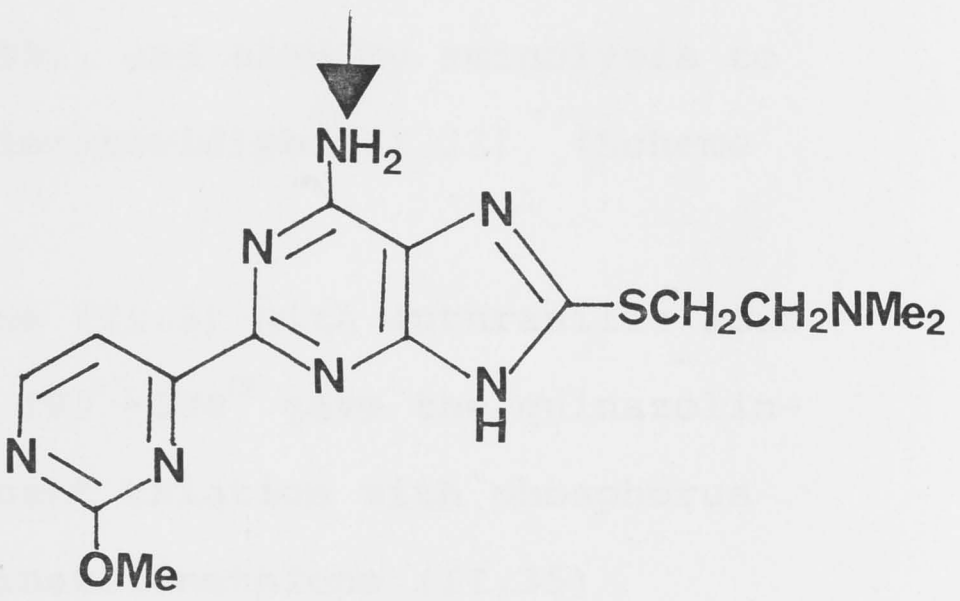
* For the position of this group see: D.J. Brown, S.-B. Lan and K. Mori, Aust. J. Chem., 37, 2093 (1984).



(II.14)



(II.26)



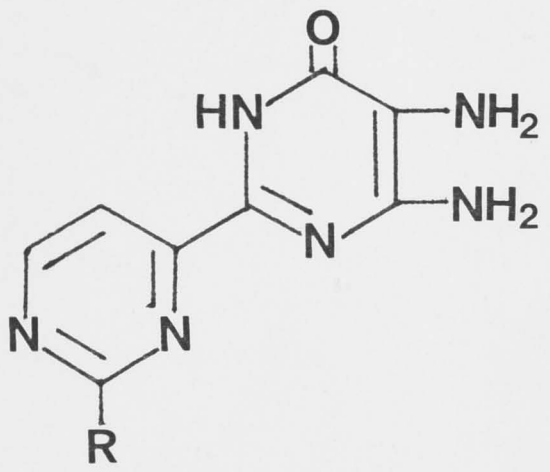
(II.27)

Scheme II-8

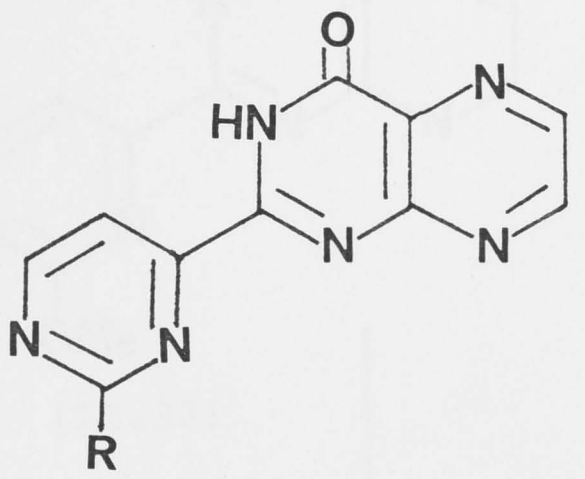
II-4 Preparation of 2-(Pyrimidin-4'-yl)-pteridines and -quinazolines, and 5-(Pyrimidin-4'-yl)-1H-v-triazolo[4,5-d]pyrimidin-7(6H)-ones

Condensation of the diaminobipyrimidinones (II.11,12) with glyoxal gave the pteridin-4-ones (II.28,29) or with nitrous acid gave the 5-(pyrimidin-4'-yl)-(1H)-v-triazolo-[4,5-d]pyrimidin-7(6H)-ones (II.30,31) (Scheme II-9). The pteridin-4-one (II.29) was converted by a mixture of phosphoryl chloride and phosphorus pentachloride into the chloropteridine (II.32), and then by aminolysis to the dimethylaminoethylaminopteridine (II.33) (Scheme II-10).

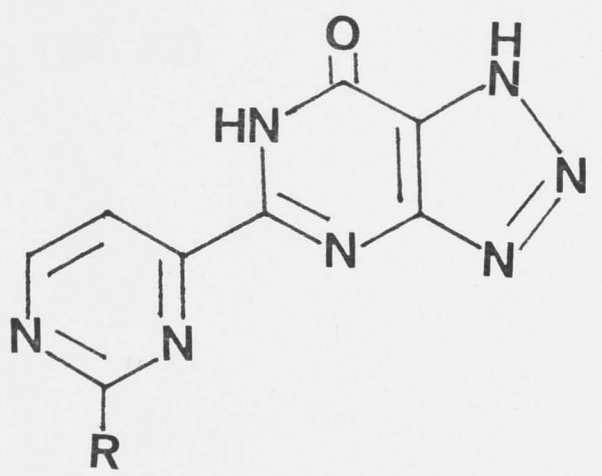
Fusion of the amidine (II.3) with anthranilic acid (o-aminobenzoic acid) at 180 -190° gave the quinazolin-4-one (II.34) and subsequent thiation with phosphorus pentasulfide gave the quinazolinethione (II.35) (Scheme II-11).



(II.11; R=NMe_2)
(II.12; R=OMe)

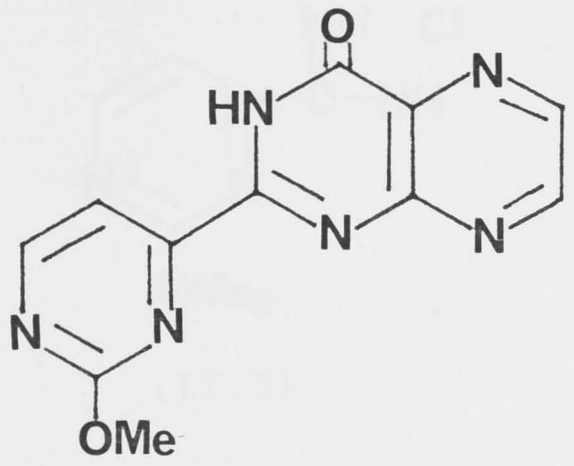


(II.28; R=NMe_2)
(II.29; R=OMe)

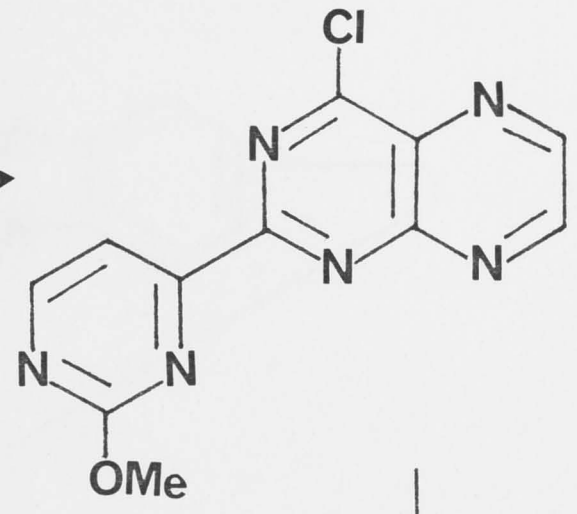


(II.30; R=NMe_2)
(II.31; R=OMe)

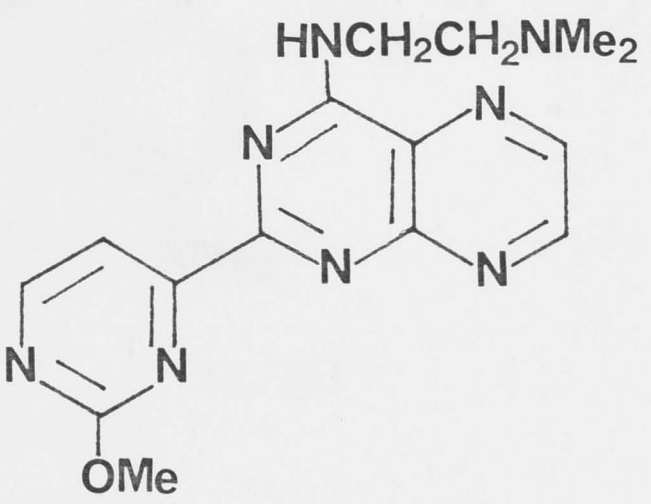
Scheme II-9



(II.29)

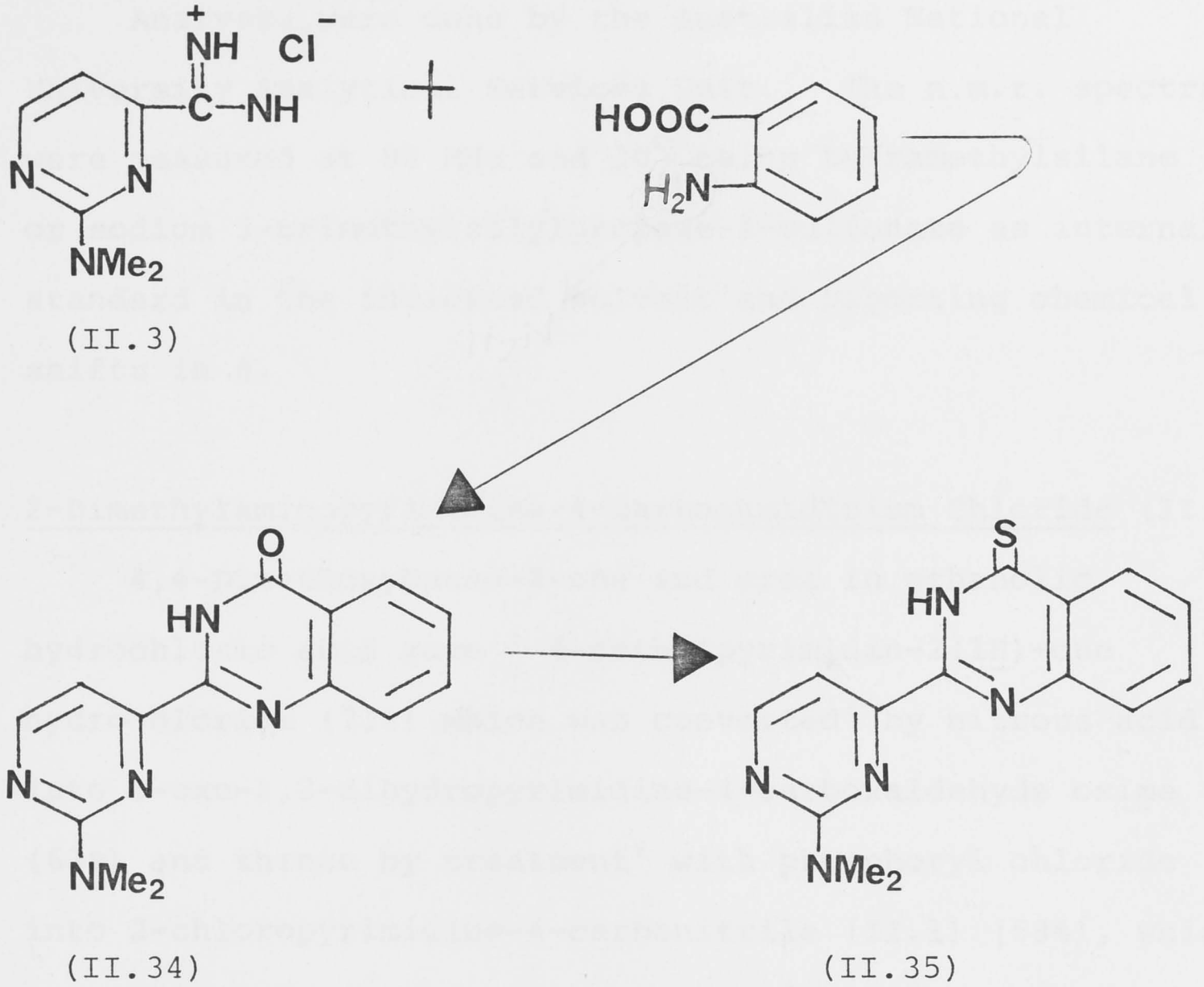


(II.32)



(II.33)

Scheme II-10



(II.3)

(II.34)

(II.35)

Scheme II-11

II-5 Experimental

Analyses (elemental) were done by the Australian National University Analytical Services Unit. The n.m.r. spectra were measured at 90 MHz and 30° using tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulfonate as internal standard in the indicated solvent and reporting chemical shifts in δ.

2-Dimethylaminopyrimidine-4-carboxamidinium Chloride (II.3)

4,4-Dimethoxybutan-2-one and urea in ethanolic hydrochloric acid gave[11] 4-methylpyrimidin-2(1H)-one hydrochloride (73%) which was converted[8] by nitrous acid into 2-oxo-1,2-dihydropyrimidine-4-carboxaldehyde oxime (63%) and thence by treatment[8] with phosphoryl chloride into 2-chloropyrimidine-4-carbonitrile (II.1) (58%), which in turn underwent dimethylaminolysis[7] to yield 2-dimethylaminopyrimidine-4-carbonitrile (II.2) (66%). This nitrile (14.8 g) and sodium methoxide (from 0.23 g of sodium) in methanol (100 ml) were stirred at 20-25° for 2 h. Then solid ammonium chloride (6.30 g) was added and stirring was continued for 2 h. The solid was filtered off and washed with a little ether prior to recrystallization from ethanol to give the amidinium chloride (81%), m.p. 285-286° (Found: C, 42.0; H, 6.1; Cl, 17.9; N, 34.4. $C_7H_{12}ClN_5$ requires C, 41.7; H, 6.0; Cl, 17.6; N, 34.7%).

2-Methoxypyrimidine-4-carboxamidinium Chloride (II.4)

2-Chloropyrimidine-4-carbonitrile (II.1)[8] (13.95 g) was added over 20 min to a stirred solution of sodium methoxide (from 2.5 g of sodium) in methanol (100 ml) at 0° and stirring was continued in the cold room for 12 h. Then ammonium chloride (6.0 g) was added and stirring was maintained at 20-25° for 12 h. Salt was removed from the crude product during recrystallization from propan-2-ol to give the methoxyamidinium chloride (86%), m.p. 210° (Found: C, 38.7; H, 4,7; Cl, 18.7; N, 29.6. $C_6H_9ClN_4O$ requires C, 38.2; H, 4.8; Cl, 18.8; N, 29.7%). N.m.r. [$(CD_3)_2SO$] 9.77, s, br, $2NH_2$; 9.04, d, H 6; 7.98, d, H 5; 4.06, s, Me.

6-Amino-2'-dimethylamino-2,4'-bipyrimidin-4(3H)-one (II.5)

The amidinium chloride (II.3) (2.0 g), ethyl cyanoacetate (1.15 g) and sodium ethoxide (from 0.5 g of sodium) in ethanol (20 ml) were heated under reflux for 6 h and then evaporated under reduced pressure. Water (50 ml) was added to the residue and the resulting solid was filtered off: it proved to be ethyl 3-amino-2-cyano-3-(2'-dimethylaminopyrimidin-4'-yl)acrylate (II.6) (43%), m.p. 143-145° (from ethanol) (Found: C, 55.3; H, 5.8; N, 26.6. $C_{12}H_{15}N_5O_2$ requires C, 55.2; H, 5.8; N, 26.8%). N.m.r. ($CDCl_3$; 25°) 8.50, d, H 6'; 7.42, d, H 5'; 4.30, q, CH_2 of Et; 3.22, s, NMe_2; 1,36, t, Me of Et. The original aqueous filtrate was adjusted to pH 5 with acetic acid and the resulting solid was recrystallized from

ethanol to give the bipyrimidinone (II.5) (42%), m.p. 305-306° (Found: C, 51.7; H, 5.3; N, 36.5. $C_{10}H_{12}N_6O$ requires C, 51.7; H, 5.2; N, 36.2%). N.m.r. ($CDCl_3$; 25°) 8.56, d, H 6'; 7.24, d, H 5'; 6.64, br, NH_2; 5.13, s, H 5; 3.21, s, NMe_2.

6-Amino-2'-dimethylamino-5-nitroso-2,4'-bipyrimidin-4(3H)-one (II.7)

(i) The foregoing bipyrimidinone (II.5) (2.32 g) in 10 M hydrochloric acid (8.0 ml) was stirred at room temperature while sodium nitrite (2.1 g) was added little by little. The mixture was diluted with water (10 ml) and stirring was continued for 1 h. The solid was filtered off and washed with a little cold water: the nitrosobipyrimidinone (73%) had m.p. 273° (dec.) (from ethanol) (Found: C, 46.3; H, 4.3; N, 37.8. $C_{10}H_{11}N_7O_2$ requires C, 45.9; H, 4.2; N, 37.5%). N.m.r. [$(CD_3)_2SO$; 25°] 9.33, br, NH_2; 8.64, d, H 6'; 7.29, d, H 5'; 3.25, s, NMe_2.

(ii) 2-Dimethylaminopyrimidine-4-carboxamidinium hydrochloride (II.3) (2.01 g), ethyl 2-cyano-2-hydroxyiminoacetate[9] (1.44 g) and sodium ethoxide (from 0.90 g of sodium) in ethanol (20 ml) were boiled under reflux for 20 h. After refrigeration, the solid was filtered off and washed with cold ethanol. It was then suspended in water (20 ml) and acidified to pH 5 by the addition of acetic acid to give the same nitrosobipyrimidinone (77%) as in (i) above.

6-Amino-2'-methoxy-5-nitroso-2,4'-bipyrimidin-4(3H)-one (II.8)

The above amidinium chloride (1.90 g), ethyl 2-cyano-2-hydroxyiminoacetate[9] (1.45 g) and sodium methoxide (from 0.95 g of sodium) in methanol (20 ml) were stirred at 20° for 15 h. The solid was treated as for the analogue (II.7) above to give the methoxynitroso derivative (82%), m.p. >240° (dec.) (from methoxyethanol) (Found: C, 43.9; H, 3.4; N, 33.7. $C_9H_8N_6O_3$ requires C, 43.6; H, 3.2; N, 33.9%).

2'-Dimethylamino-5-nitroso-2,4'-bipyrimidine-4,6-diamine (II.9)

The silver salt of α-hydroxyiminomalononitrile[10] (2.2 g) was added little by little to a stirred solution of 2-dimethylaminopyrimidine-4-carboxamidinium chloride (II.3) (2.0 g) in methanol (100 ml) at room temperature. After stirring for a further 60 min, silver chloride was filtered off and the filtrate was evaporated to dryness at 20-25° under reduced pressure. The residual salt was boiled under reflux in 2-methylpyridine (15 ml) for 15 min and the cooled reaction mixture was diluted with ice–water. Refrigeration gave the dimethylaminobipyrimidine (II.9) (84%), m.p. 324-326° (from 2-methoxyethanol) (Found: C, 46.3; H, 4.4; N, 43.2. $C_{10}H_{12}N_8O$ requires C, 46.2; H, 4.6; N, 43.1%). N.m.r. [$(CD_3)_2SO$] 8.50, d, H 6'; 7.22, d, H 5'; 3.18, s, NMe_2.

2'-Methoxy-5-nitroso-2,4'-bipyrimidine-4,6-diamine (II.10)

In a similar way, 2-methoxypyrimidine-4-carboxamidinium chloride (II.4) (1.9 g) gave the hygroscopic methoxybipyrimidine (78%), m.p. 289° (dec.) (Found: C, 39.5; H, 4.0; N, 35.4. $C_9H_9N_7O_2.1.5\ H_2O$ requires C, 39.4; H, 4.4; N, 35.7%). N.m.r. [$(CD_3)_2SO$] 8.80, d, H 6'; 7.82, d, H 5'; 3.98, s, OMe.

5,6-Diamino-2'-dimethylamino-2,4'-bipyrimidin-4(3H)-one (II.11)

The nitroso compound (II.7) (13.05 g) was stirred in 1 M sodium hydroxide (200 ml) at 60° while sodium dithionite (c. 15-20 g) was added until the suspension became a solution and no further colour change occurred. The solution was boiled gently for 10 min, and then neutralized with acetic acid and cooled to 15° to complete precipitation of the diaminobipyrimidinone (82%), m.p. >220° (dec.) (from aqueous methanol) (Found: C, 43.5; H, 5.5; N, 39.4. $C_{10}H_{13}N_7O$ requires C, 43.6; H, 5.3; N, 39.6%). N.m.r. [$(CD_3)_2SO$] 8.52, d, H 6'; 7.22, d, H 5'; 6.70, s, NH_2; 5.91, s, NH_2; 3.22, s, NMe_2.

5,6-Diamino-2'-methoxy-2,4'-bipyrimidin-4(3H)-one (II.12)

The nitroso compound (II.8) (12.4 g) was reduced exactly as for analogue (II.11) above. The crude product was purified by dissolution in hot aqueous ammonia and reprecipitation with acetic acid followed by appropriate washing. The diamine (80%) had m.p. >264°

(dec.) (Found: C, 45.9; H, 4.3; N, 35.7. $C_9H_{10}N_6O_2$ requires C, 46.2; H, 4.3; N, 35.9%).

2'-Dimethylamino-2,4'-bipyrimidine-4,5,6-triamine (II.13)

The nitroso derivative (II.9) (1.0 g), sodium dithionite (4.0 g) and 1 M sodium hydroxide (40 ml) were heated under reflux for 1 h. Chilling gave the dimethylaminotriamine (82%), m.p. 269-270° (from ethanol) (Found: C, 48.4; H, 5.9; N, 45.5. $C_{10}H_{14}N_8$ requires C, 48.8; H, 5.7; N, 45.5%). N.m.r. [$(CD_3)_2SO$] 8.32, d, H 6'; 7.22, d, H 5'; 5.74, s, 4 + 6-NH_2; 4.23, s, 5-NH_2; 3.46, s, NMe_2.

2'-Methoxy-2,4'-bipyrimidine-4,5,6-triamine (II.14)

The nitroso compound (II.10) was reduced similarly, but in pyridine (40 ml) with heating for 6 h. The cooled solution was filtered from inorganic matter and subsequent evaporation under reduced pressure gave the methoxytriamine (85%), m.p. 232-233° (from ethanol) (Found: C, 46.4; H, 4.9; N, 42.0. $C_9H_{11}N_7O$ requires C, 46.3; H, 4.8; N, 42.0%). N.m.r. [$(CD_3)_2SO$] 8.56, d, H 6'; 7.73, d, H 5'; 5.81, s, 4 + 6-NH_2; 4.36, s, 5-NH_2; 3.94, s, OMe.

2-(2'-Dimethylaminopyrimidin-4'-yl)purin-6(1H)-one (II.15)

The diamine (II.11) (2.47 g), triethyl orthoformate (18.0 ml) and acetic anhydride (12.5 ml) were boiled under reflux for 15 min and then evaporated to dryness.

Recrystallization of the residue from a large volume of chloroform with subsequent concentration gave the purinone (93%), m.p. 348° (dec.) (Found: C, 51.5; H, 4.3; N, 38.0. $C_{11}H_{11}N_7O$ requires C, 51.4; H, 4.3; N, 38.1%).

2-(2'-Methoxypyrimidin-4'-yl)purin-6(1H)-one (II.16)

The diamine (II.12) (2.34 g) was converted, as for the analogue (II.15) into the methoxypyrimidinylpurinone (85%), m.p. >308° (dec.) (from methoxyethanol) (Found: C, 49.3; H, 3.2; N, 34.5. $C_{10}H_8N_6O_2$ requires C, 49.2; H, 3.3; N, 34.4%). N.m.r. [$(CD_3)_2SO$] 8.85, d, H 6'; 8.28, s, H 8; 7.93, d, H 5'; 4.11, s, Me.

6-Chloro-2-(2'-dimethylaminopyrimidin-4'-yl)purine (II.17)

The purinone (II.15) (2.57 g) and phosphoryl chloride (25 ml) were heated under reflux for 2 h. The excess of phosphoryl chloride was removed under reduced pressure and the residue was stirred thoroughly with crushed ice. The solution was adjusted to pH 5 at 0-5°. The solid was filtered off and washed with a little water prior to drying in a vacuum; subsequent recrystallization from methoxyethanol gave the chloropurine (58%), m.p. 204° (Found: C, 47.7; H, 3.8; Cl, 12.7; N, 35.4. $C_{11}H_{10}ClN_7$ requires C, 47.9; H, 3.7; Cl, 12.9; N, 35.6%). N.m.r. [$(CD_3)_2SO$] 8.77, s, H 8; 8.54, d, H 6; 7.47, d, H 5; 3.23, s, NMe_2.

6-Chloro-2-(2'-methoxypyrimidin-4'-yl)purine (II.18)

The above purinone (II.16) (2.44 g) was treated with phosphoryl chloride as for the analogue (II.17) to give the chloropurine (63%), m.p. >360° (from glacial acetic acid) (Found: C, 45.7; H, 2.9; N, 32.0. $C_{10}H_7ClN_6O$ requires C, 45.7; H, 2.7; N, 32.0%).

2-(2'-Dimethylaminopyrimidin-4'-yl)purine-6(1H)-thione (II.19)

The chloropurine (II.17) (2.76 g), thiourea (1.0 g) and ethanol (25 ml) were boiled under reflux for 30 min. After refrigeration, the solid was recrystallized from methoxyethanol to give the purinethione (83%), m.p. >325° (dec.) (Found: C, 48.2; H, 4.2; N, 35.8; S, 11.9. $C_{11}H_{11}N_7S$ requires C, 48.3; H, 4.1; N, 35.9; S, 11.7%).

N,N-Dimethyl-4-(6'-methylthiopurin-2'-yl)pyrimidin-2-amine (II.20)

The pyrimidinethione (II.19) (2.73 g) was dissolved in 2 M sodium hydroxide (20 ml) and the solution was shaken with methyl iodide (2.0 g) for 2 h at 20-25°. The chilled mixture was adjusted to pH 5 with acetic acid and the product was filtered off. The methylthiopurine (74%) had m.p. 307° (from methoxyethanol) (Found: C, 49.9; H, 4.4; N, 33.7; S, 11.0. $C_{12}H_{13}N_7S$ requires C, 50.2; H, 4.6; N, 34.1; S, 11.2%).

2-[2'-(2"-Dimethylaminopyrimidin-4"-yl)purine-6'-ylthio]-N,N-dimethylethylamine (II.21)

A solution of the purinethione (II.19) (2.73 g) in 2 M sodium hydroxide (20 ml) was stirred while 2-chloro-N,N-dimethylethylammonium chloride (1.70 g) was added over 10 min. After stirring for a further 2 h, the mixture was extracted with chloroform (3 x 40 ml). The dehydrated extract was evaporated to give the purinylthioethylamine (57%), m.p. 206-207° (from ethyl acetate) (Found: C, 52.2; H, 5.7; N, 32.1; S, 9.4. $C_{15}H_{20}N_8S$ requires C, 52.3; H, 5.8; N, 32.5; S, 9.3%). N.m.r. ($CDCl_3$; 25°) 8.59, d, H 6"; 8.02, s, H 8'; 7.72, d, H 5"; 3.64, t, H 2; 3.28, s, 2"-NMe_2; 2.78, t, H 1; 2.38, s, 1-NMe_2.

N-(2"-Dimethylaminoethyl)-2-(2'-methoxypyrimidin-4'-yl)-purin-6-amine (II.22)

The chloropurine (II.18) (1.0 g) and 2-dimethylaminoethylamine (5.0 ml) were boiled under reflux for 1 h. The residue, from removal of the excess of amine under reduced pressure, was added to 2 M sodium hydroxide (5.0 ml) and extracted with chloroform. Evaporation of the dried extract gave the purinamine (42%), m.p. 185-186° (from propan-2-ol) (Found: C, 53.8; H, 5.8; N, 35.7. $C_{14}H_{18}N_8O$ requires C, 53.5; H, 5.8; N, 35.6%).

6-Amino-2-(2'-dimethylaminopyrimidin-4'-yl)purine-8(7H)-thione (II.23)

The triamine (II.13) (1.0 g) and thiourea (1.20 g) were ground together and then fused at 220° for 1 h. A solution of the cooled mixture in 2 M sodium hydroxide was decolourized with carbon and acidified with hydrochloric acid to give the purinethione (68%), m.p. 251° (dec.) (from glacial acetic acid) (Found: C, 45.9; H, 4.3; N, 38.7; S, 10.8. $C_{11}H_{12}N_8S$ requires C, 45.8; H, 4.2; N, 38.9; S, 11.1%). N.m.r. [$(CD_3)_2SO$] 8.53, d, H 6'; 7.36, d, H 5'; 3.28, s, NMe_2.

8-(2"-Dimethylaminoethyl)thio-2-(2'-dimethylaminopyrimidin-4'-yl)purin-6-amine (II.24)

2-Chloro-N,N-dimethylethylamine hydrochloride (0.8 g) was added over 10 min to a stirred solution of the purinethione (II.23) (1.0 g) in 2 M sodium hydroxide (20 ml) at room temperature. Stirring was continued for a further 2 h and the alkaline solution was then adjusted to pH 8 with hydrochloric acid. Extraction with chloroform, dehydration of the extract, and evaporation thereof gave the purinamine (II.24) (61%), m.p. 236° (from ethyl acetate) (Found: C, 49.9; H, 6.0; N. 35.0. $C_{15}H_{21}N_9S$ requires C, 50.1; H, 5.9; N, 35.1%). N.m.r. ($CDCl_3$) 8.46, d, H 6'; 7.48, d, H 5'; 5.59, br, NH_2; 3.29, s, 2'-NMe_2; 3.11, t, H 1"; 2.87, t, H 2"; 2.45, s, 2"-NMe_2.

N-[9-Acetyl-8-(2"-dimethylaminoethyl)thio-2-(2'-dimethylaminopyrimidin-4'-yl)purin-6-yl]acetamide (II.25)

The purinamine (II.24) (0.3 g) and acetic anhydride (5.0 ml) were heated under reflux for 5 h. The excess of anhydride was distilled off under reduced pressure to leave the diacetyl derivative (II.25) (62%), m.p. 216° (from ethanol) (Found: C, 51.1; H, 5.8; N, 28.5; $C_{19}H_{35}N_9O_2S$ requires C, 51.4; H, 5.7; N, 28.4%). N.m.r. ($CDCl_3$) 8.50, d, H 6'; 8.36, br, NH; 7.45, d, H 5'; 3.44, t, H 1"; 3.29, s, 2'-NMe_2; 3.15, s, 9-Ac; 2.89, s, Me of NHAc; 2.74, t, H 2"; 2.33, 3, 2"-NMe_2.

6-Amino-2-(2'-methoxypyrimidin-4'-yl)purine-8(7H)-thione (II.26)

The triamine (II.14) (1.0 g), carbon disulfide (1.5 g), solid sodium hydroxide (0.20 g) and pyridine (20 ml) were heated under reflux for 1 h. The cooled mixture was diluted with 1.25 M hydrochloric acid. The resulting solid was decolourized as above to give the thione (II.26) (71%), m.p. 230° (dec.) (from glacial acetic acid) (Found: C, 43.9; H, 3.4; N, 35.3. $C_{10}H_9N_7OS$ requires C, 43.6; H, 3.3; N, 35.6%). N.m.r. [$(CD_3)_2SO$] 8.72, d, H 6'; 7.83, d, H 5'; 7.42, br, NH_2; 3.98, s, OMe.

8-(2"-Dimethylaminoethyl)thio-2-(2'-methoxypyrimidin-4'-yl)purin-6-amine (II.27)

In a similar way to (II.24), apart from stirring at 60° for only 30 min, the purinethione (II.26) was converted into the purinamine (54%), m.p. 213° (from ethanol) (Found: C, 48.4; H, 5.2; N, 32.2. $C_{14}H_{18}N_8OS$ requires C, 48.5; H, 5.2; N, 32.4%). N.m.r. [$(CD_3)_2SO$] 8.69, d, H 6'; 7.88, d, H 5'; 7.00, br, NH_2; 3.99, s, OMe; 3.43, t, H 2"; 2.68, t, H 2"; 2.25, s, NMe_2.

2-(2'-Dimethylaminopyrimidin-4'-yl)pteridin-4(3H)-one (II.28)

The diamine (II.11) (2.47 g), aqueous glyoxal (40%; 1.5 ml) and ethanol (20 ml) were heated under reflux for 30 min. Refrigeration gave the pteridinone (76%), m.p. 266-267° (from dimethylformamide) (Found: C, 53.6; H, 4.1; N, 36.4. $C_{12}H_{11}N_7O$ requires C, 53.5; H, 4.1; N, 36.4%). N.m.r. ($CDCl_3$) 9.02, d, H 6; 8.88, d, H 7; 8.63, d, H 6'; 7.75, d, H 5'; 3.30, s, NMe_2.

2-(2'-Methoxypyrimidin-4'-yl)pteridin-4(3H)-one (II.29)

The diamine (II.12) (2.34 g), aqueous glyoxal (40%; 2.0 ml) and water (20 ml) were warmed on the water bath for 15 min. Refrigeration gave the pteridinone (92%), m.p. >278° (dec.) (from dimethylformamide)

(Found: C, 51.4; H, 3.1; N, 32.7. $C_{11}H_8N_6O_2$ requires C, 51.6; H, 3.1; N, 32.8%). N.m.r. [$(CD_3)_2SO$] 9.08, d, H 6; 8.93, d, H 7; 8.92, d, H 6'; 8.05, d, H 5'; 4.14, s, Me.

5-(2'-Dimethylaminopyrimidin-4'-yl)-(1H)-v-triazolo[4,5-d]-pyrimidin-7(6H)-one (II.30)

Sodium nitrite (0.5 g) was added over 10 min to a stirred solution of 5,6-diamino-2'-dimethylamino-2,4'-bipyrimidin-4(3H)-one (II.11) (1.0 g) in 2 M hydrochloric acid (10 ml) at 0°. Stirring was continued at 0° for 30 min and then at 25° for 2 h, after which the triazolopyrimidinone (II.30) (63%) was filtered off and washed with iced water. It has m.p. 304° (Found: C, 46.8; H, 4.3; N, 43.3. $C_{10}H_{10}N_8O$ requires C, 46.5; H, 3.9; N, 43.4%). N.m.r. ($NaOD/D_2O$) 8.34, d, H 6'; 7.26, d, H 5'; 3.14, s, NMe_2.

5-(2'-Methoxypyrimidin-4'-yl)-(1H)-v-triazolo[4,5-d]-pyrimidin-7(6H)-one (II.31)

In a similar way, 5,6-diamino-2'-methoxy-2,4'-bipyrimidin-4(3H)-one (II.12) gave the triazolopyrimidinone (II.31) (54%), m.p. 308° (dec.) (Found: C, 44.3; H, 2.9; N, 39.6. $C_9H_7N_7O$ requires C, 44.1; H, 2.9; N, 40.0%). N.m.r. ($NaOD/D_2O$) 8.52, d, H 6'; 7.75, d, H 5'; 4.01, s, OMe.

4-Chloro-2-(2'-methoxypyrimidin-4'-yl)pteridine (II.32)

The pteridinone (II.29) (1.0 g), phosphoryl chloride (50 ml) and phosphorus pentachloride (1.0 g) were boiled under reflux for 4 h. The phosphoryl chloride was distilled off under reduced pressure and the residue was stirred into crushed ice and allowed to stand at 5° for 15 h. Filtration gave the chloropteridine (II.32) (72%), m.p. 232-233° (from methanol) (Found: C, 47.8; H, 2.6; Cl, 12.5; N, 30.6. $C_{11}H_7ClN_6O$ requires C, 48.1; H, 2.6; Cl, 12.9; N, 30.6%). N.m.r. [$(CD_3)_2SO$] 9.06, d, H 6; 8.92, d, H 7; 8.90, d, H 6'; 8.05, d, H 5'; 4.14, s, Me.

N-(2"-Dimethylaminoethyl)-2-(2'-methoxypyrimidin-4'-yl)-pteridin-4-amine (II.33)

The foregoing chloropteridine (1.0 g) and 2-dimethylaminoethylamine (6.0 ml) were heated under reflux for 1 h. The residue from distilling off the excess of amine under reduced pressure was diluted with 2 M sodium hydroxide and the mixture was extracted with chloroform. Evaporation of the extract gave the pteridinamine (34%), m.p. 158-159° (from propan-2-ol) (Found: C, 54.9; H, 5.6; N, 34.0. $C_{15}H_{18}N_8O$ requires C, 55.2; H, 5.6; N, 34.3%). N.m.r. ($CDCl_3$) 9.06, d, H 6; 8.72, d, H 7; 8.70, d, H 6'; 8.18, d, H 5'; 7.82, br, NH; 4.16, s, OMe; 3.90, q, H 1"; 2.67, t, H 2"; 2.17, s, NMe_2.

2-(2'-Dimethylaminopyrimidin-4'-yl)quinazolin-4(3H)-one (II.34)

2-Dimethylaminopyrimidine-4-carboxamidinium chloride (II.3) (1.5 g) and anthranilic acid (0.5 g) were fused together at 180° for 1 h. The cooled mixture was triturated with a little water and filtration gave the quinazolinone (62%), m.p. 248° (from ethanol) (Found: C, 62.3; H, 4.8; N, 25.8. $C_{14}H_{13}N_5O$ requires C, 62.9; H, 4.9; N, 26.2%). N.m.r. (NaOD/D_2O) 8.29, d, H 6'; 7.69, m, H 5-8; 7.18, d, H 5'; 3.11, s, NMe_2.

2-(2'-Dimethylaminopyrimidin-4'-yl)quinazolin-4(3H)-thione (II.35)

The quinazolinone (II.34) (0.5 g), phosphorus pentasulfide (0.6 g) and pyridine (30 ml) were heated under reflux for 2 h. The cooled mixture was poured into ice water (150 ml) and refrigeration gave the quinazolinethione (57%), m.p. 232° (from ethanol) (Found: C, 59.0; H, 4,6; N, 24.4. $C_{14}H_{13}N_5S$ requires C, 59.3; H, 4.6; N, 24.7%). N.m.r. ($CDCl_3$) 8.78, d, H 6'; 8.58, d, H 5'; 7.73, m, H 5-8; 3.32, s, NMe_2.

REFERENCES

1. D. J. Brown, B. B. Buttler, W. B. Cowden, G. W. Grigg, D. Kavulak, and D. M. Podger, Aust. J. Chem., 34, 2423 (1981).

2. D. J. Brown and W. B. Cowden, Aust. J. Chem., 35, 1203 (1982); 36, 1469 (1983).

3. D. J. Brown, W. B. Cowden, and L. Strekowski, Aust. J. Chem., 35, 1209 (1982).

4. D. J. Brown and G. W. Grigg, Med. Res. Rev., 2, 193 (1982).

5. D. J. Brown, G. W. Grigg, Y. Iwai, K. N. McAndrew, T. Nagamatsu, and R. van. Heeswyck, Aust. J. Chem., 32, 2713 (1979).

6. D. J. Brown, W. C. Dunlap, G. W. Grigg, and L. Danckwerts, Aust. J. Chem., 31, 447 (1978).

7. D. J. Brown, W. B. Cowden, and L. Strekowski, Aust. J. Chem., 34, 1351 (1981).

8. G. D. Daves, D. E. O'Brien, L. R. Lewis, and C. C. Cheng, J. Heterocycl. Chem., 1, 130 (1963).

9. M. Conrad and A. Schultz, Ber. Dtsch. Chem. Ges., 42, 735 (1909).

10. G. Longo, Gazz. Chim. Ital., 61, 575 (1931).

11. D. M. Burness, J. Org. Chem., 21, 97 (1956).

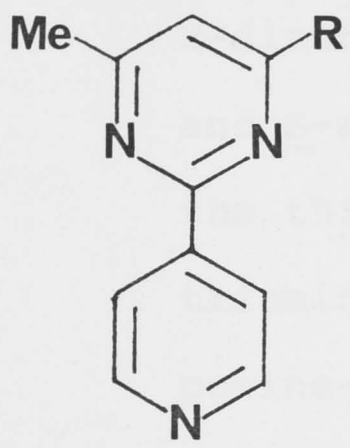
CHAPTER III

SYNTHESIS OF SOME PHENYLPURINES, PHENYLPTERIDINES, AND PHENYLQUINAZOLINES

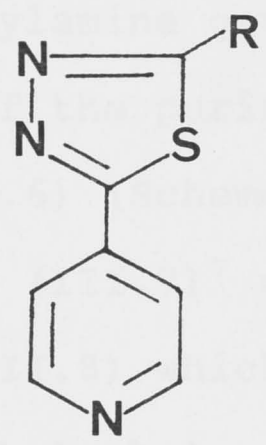
III-1 Introduction

Unfused heterobicycles, such as N,N-dimethyl-2-[6'-methyl-2'-(pyridin-4"-yl)pyrimidin-4'-ylthio]-ethylamine (III.1a), N,N-dimethyl-2-[5'-pyridin-4"-yl)-1',3',4'-thiadiazol-2'-ylthio]ethylamine (III.1b), and in particular N,N-dimethyl-2-(6'-methyl-2'-phenyl-pyrimidin-4'-ylthio)ethylamine (III.2) (Scheme III-1) have been reported elsewhere as having high activities as amplifiers of phleomycins against E. coli in vitro and also (for two of the above) against tumors in vivo.[1-4]

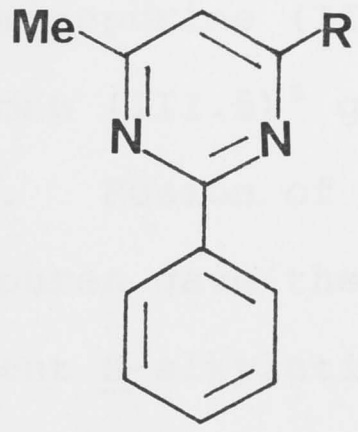
In view of the fact that fused heterobicycles such as purines have also shown quite high activity, it seemed worthwhile to prepare appropriate phenylpurines, phenylpteridines and phenylquinazolines. In effect, these systems amount to the annelation of an imidazole, pyrazine and benzene ring to the pyrimidine ring of the above-mentioned highly active phenylpyrimidines.



(III.1a)



(III.1b)



(III.2)

$R = SCH_2CH_2NMe_2$

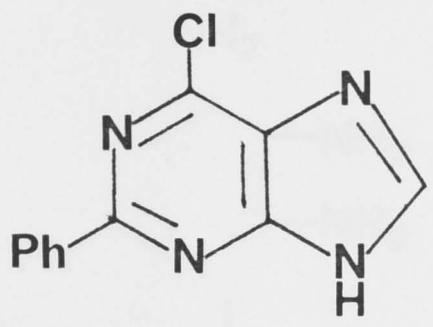
(Scheme III-1)

III-2 Preparation of Phenylpurine Derivatives

Aminolysis of 6-chloro-2-phenylpurine (III.3)[5] with 2-dimethylaminoethylamine gave the aminopurine (III.4), and S-alkylation of the purine-6-thione (III.5)[6] gave the thioether (III.6) (Scheme III-2). Fusion of the triaminopyrimidine (III.7)[7] with thiourea gave the purine-8-thione (III.8) which underwent S-alkylation by 2-chloro-N,N-dimethylethylamine to give the thioether (III.9) (Scheme III-3). Methylation of the pyrimidine-2-thione (III.10)[8] with methyl iodide gave the methylthiopyrimidine (III.11) which underwent condensation with dimethoxymethyl acetate to give the 2-methylthiopurine (III.12) (Scheme III-4).

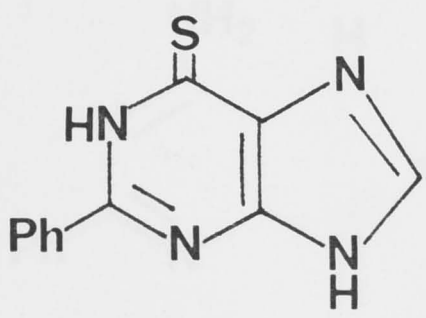
Dithionite reduction of nitroso compound (III.14), which was prepared by condensation of the pyridine-4-carboxamidinium chloride (III.13)[9] with ethyl 2-cyano-2-hydroxyiminoacetate gave the pyrimidinediamine (III.15) (Scheme III-5). This was converted by triethyl orthoformate in acetic anhydride into the pyridinyl-hypoxanthine, (III.16) and thence by phosphorus pentasulfide into the purine-6-thione (III.17) which underwent S-alkylation to give the thioether (III.18).

S-Alkylation of 8-phenylpurine-6-thione (III.19)[10] with 2-chloro-N,N-dimethylethylamine gave the thioether (III.20) (Scheme III-6). 2-Chloro-8-phenylpurine (III.25) was prepared by two methods: (i) oxidative cyclization (with NBS) of the 5-benzylideneamino-2-chloropyrimidine (III.22), which was obtained by the reaction of 2-chloropyrimidine-4,5-diamine (III.21)[11] with benzaldehyde; (ii) cyclization and

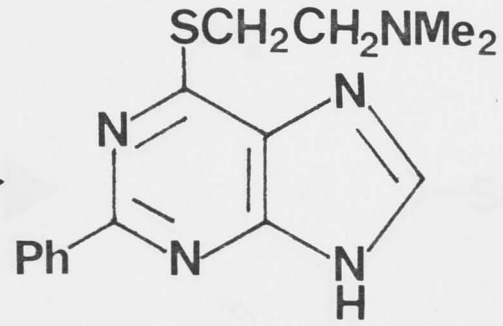


(III.3)

(III.4)

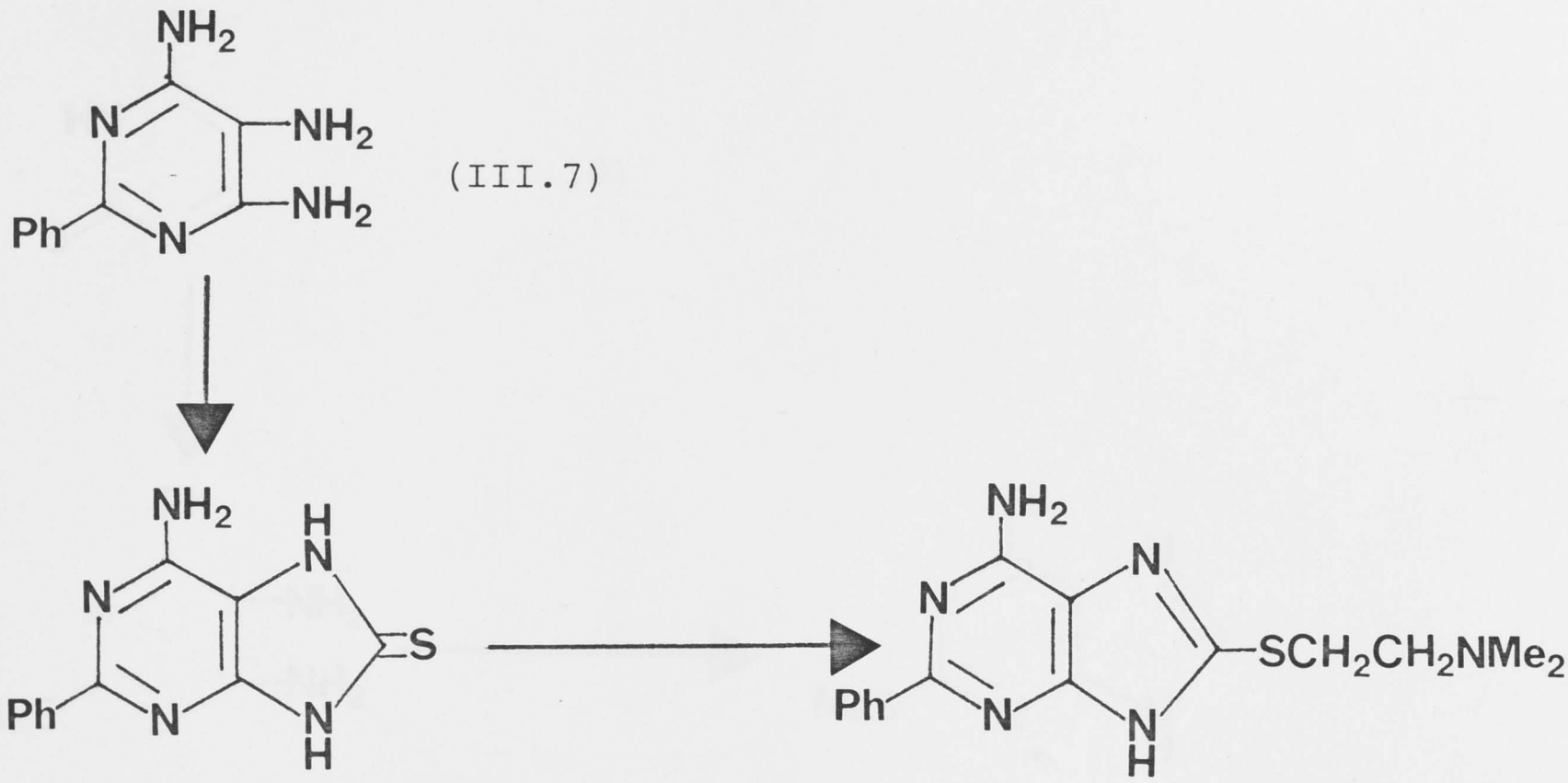


(III.5)

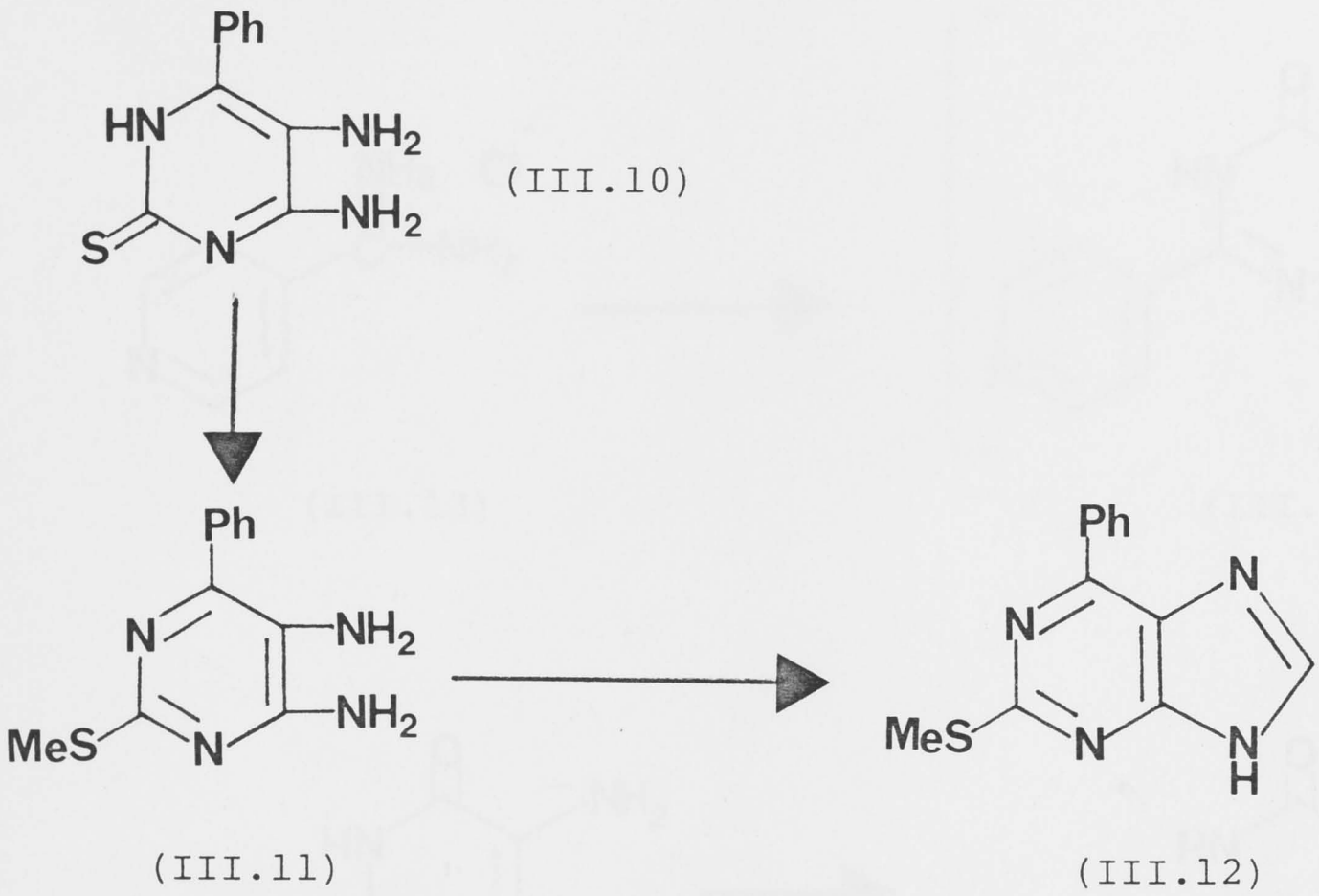


(III.6)

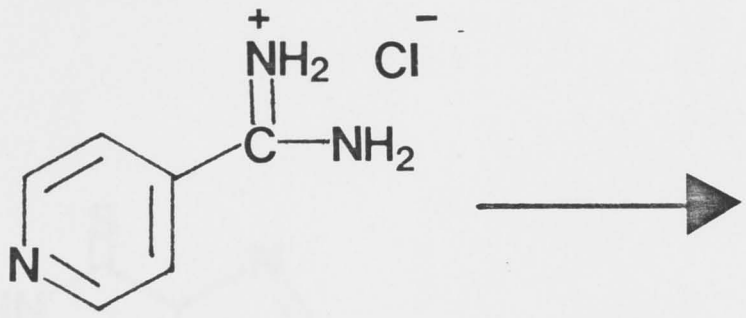
(Scheme III-2)


NH2
N
NH2
NH2
Ph
N
(III.7)
NH2
H
N
N
S
Ph
N
N
H
(III.8)
NH2
N
N
N
SCH2CH2NMe2
Ph
N
N
H
(III.9)

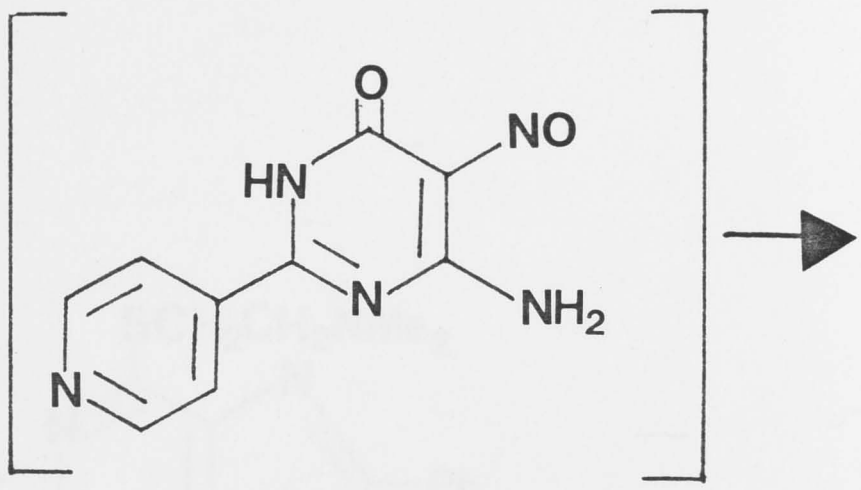
(Scheme III-3)


Ph
HN
NH2
NH2
S
N
(III.10)
Ph
N
NH2
NH2
MeS
N
(III.11)
Ph
N
N
MeS
N
N
H
(III.12)

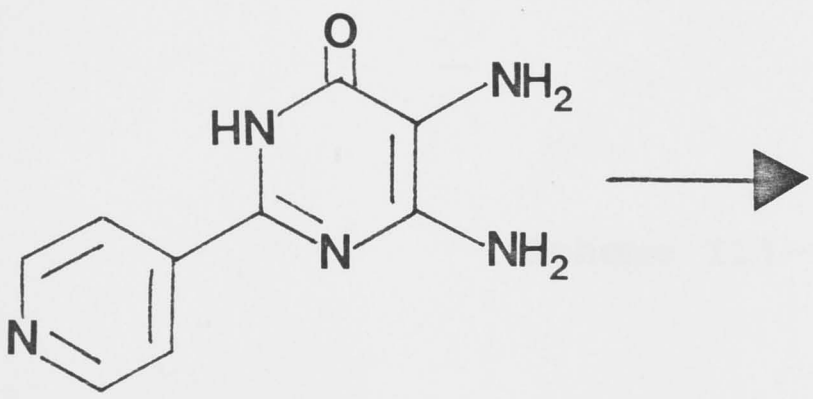
(Scheme III-4)



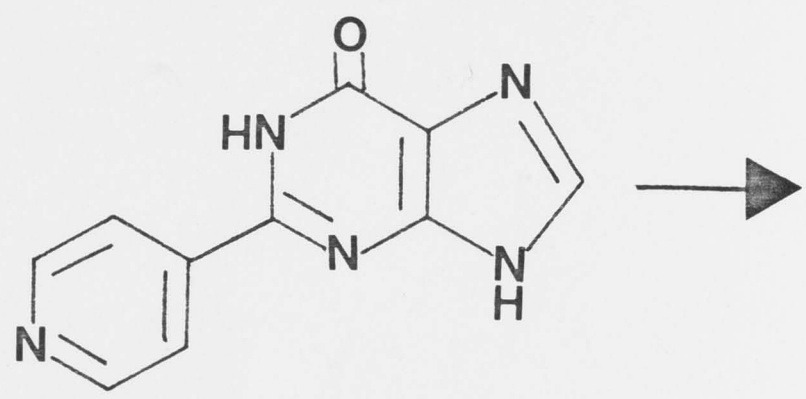
(III.13)



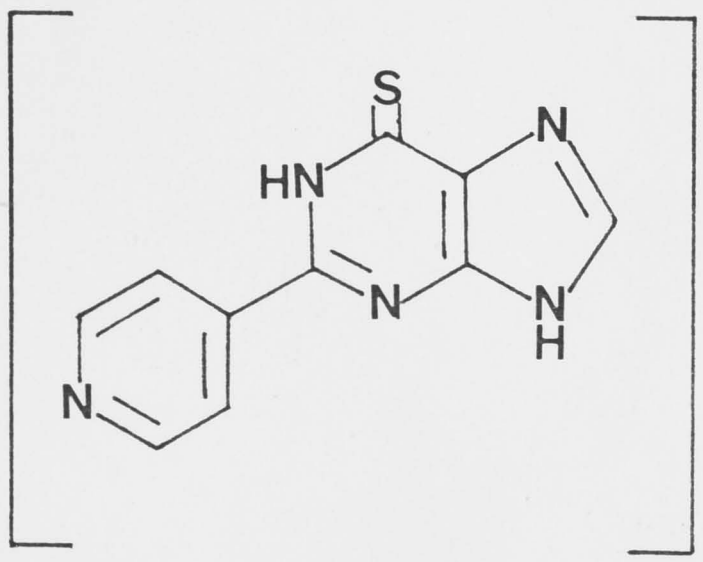
(III.14)



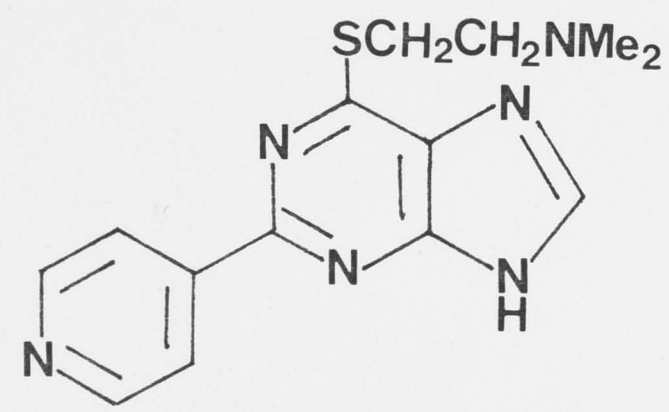
(III.15)



(III.16)

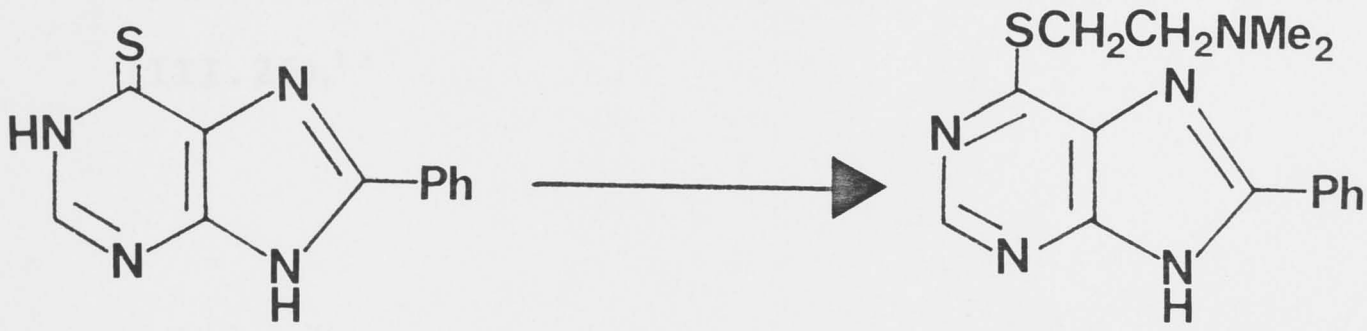


(III.17)



(III.18)

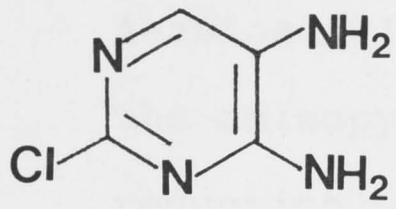
(Scheme III-5)



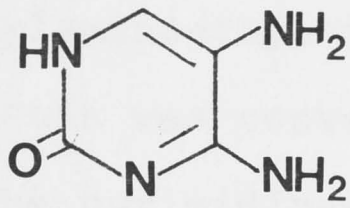
(III.19) (III.20)

(Scheme III-6)

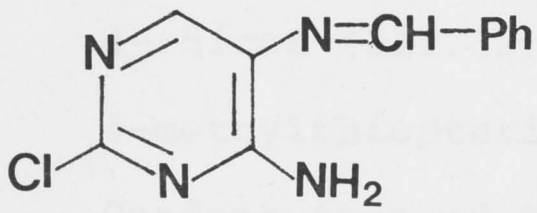
chlorination of the 5-benzamidopyrimidin-2-one (III.24) which was obtained by the reaction of 4,5-diamino-pyrimidin-2-one (III.23)[12] with benzoyl chloride. (Scheme III-7). This chloro compound (III.25) was then converted by thiourea into the purine-2-thione (III.26).[13]



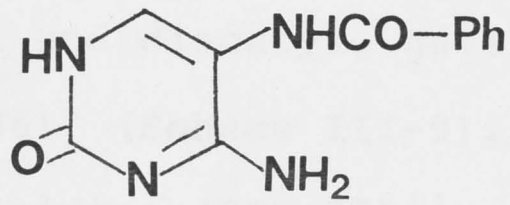
(III.21)



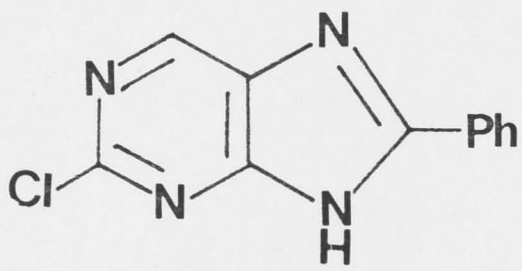
(III.23)



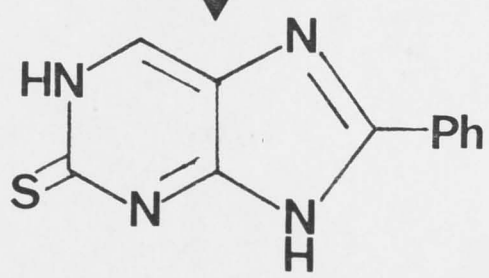
(III.22)



(III.24)



(III.25)

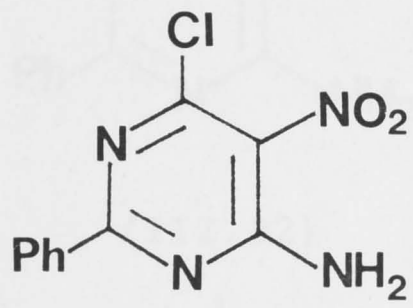


(III.26)

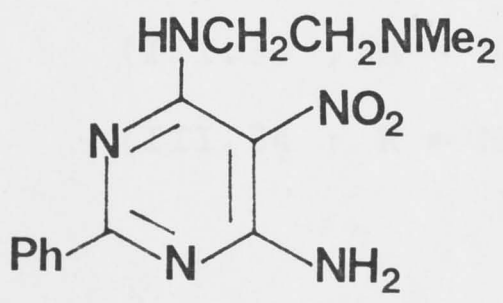
(Scheme III-7)

III-3 Preparation of Phenylpteridine Derivatives

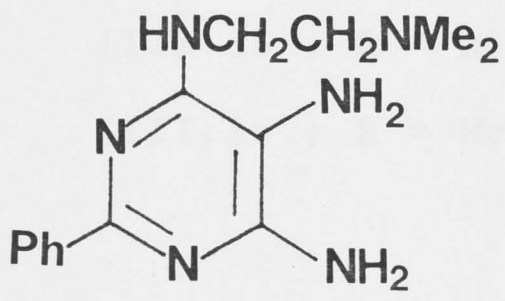
Aminolysis of 6-chloro-5-nitro-2-phenylpyrimidin-4-amine (III.27)[14] with 2-dimethylaminoethylamine gave the aminopyrimidine (III.28). This was converted by reduction with dithionite into the pyrimidine-4,5-diamine (III.29) and subsequent condensation with glyoxal and diacetyl gave the pteridines (III.30,31) (Scheme III-8). Methylation of the pteridine-4-thiones (III.33,34), obtained by condensation of the pyrimidine-4-thione (III.32)[14] with glyoxal and diacetyl, gave the 4-methylthiopteridines (III.35,36) (Scheme III-9). Condensation of the 2-chloropyrimidine (III.37)[11] and 2-methylthiopyrimidine (III.11) with glyoxal and diacetyl gave the 2-chloropteridine (III.38) and the 2-methylthiopteridines (III.39,40) (Scheme III-10).



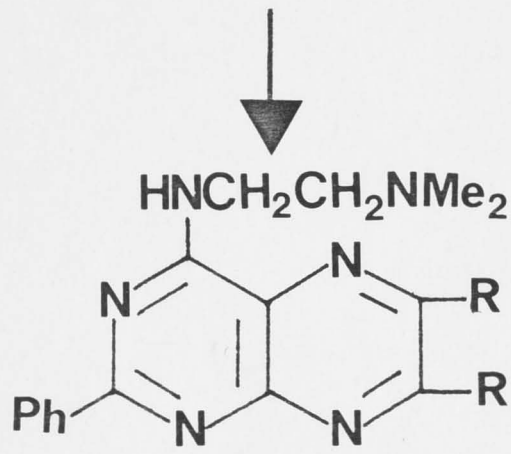
(III.27)



(III.28)



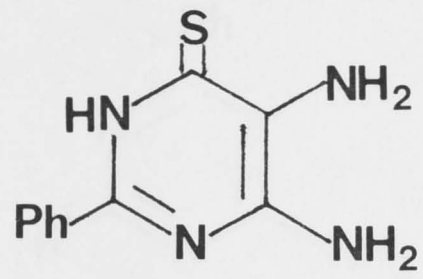
(III.29)



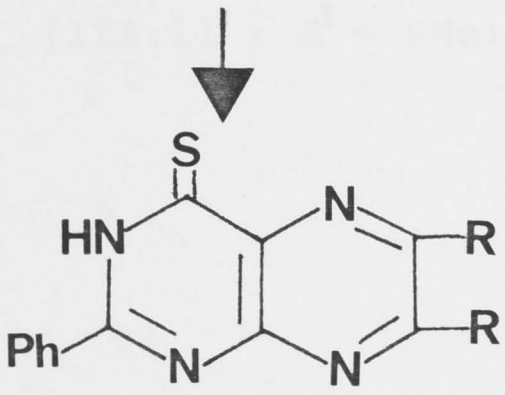
(III.30 ; R = H)

(III.31 ; R = Me)

(Scheme III-8)

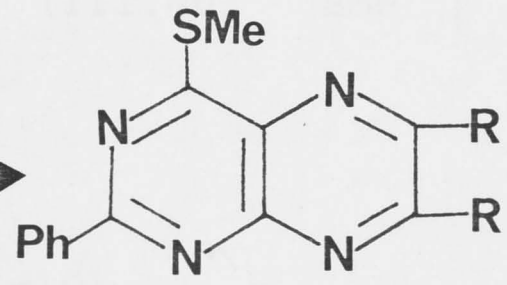


(III.32)



(III.33 ; R = H)

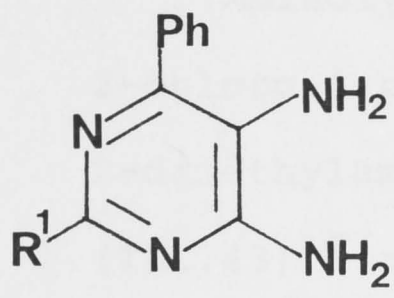
(III.34 ; R = Me)

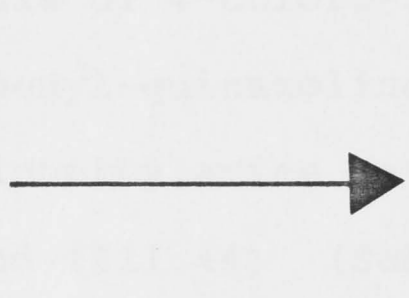


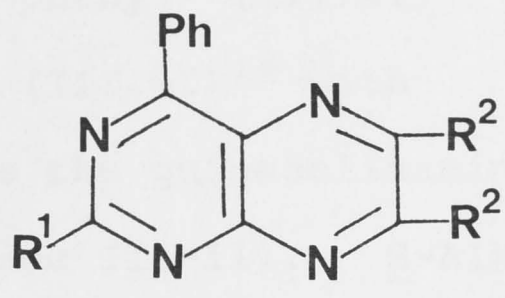
(III.35 ; R = H)

(III.36 ; R = Me)

(Scheme III-9)







(III.37 ; R^1 = Cl)

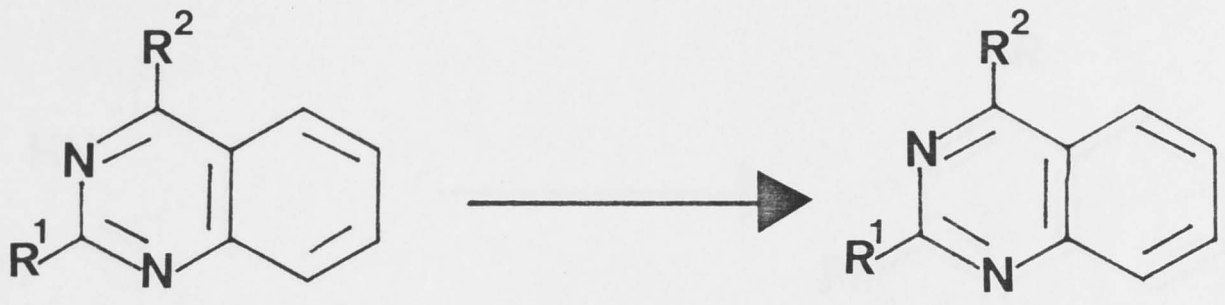
(III.11 ; R^1 = SMe)

	R^1	R^2
(III.38)	Cl	Me
(III.39)	SMe	H
(III.40)	SMe	Me

(Scheme III-10)

III-4 Preparation of Phenylquinazoline Derivatives

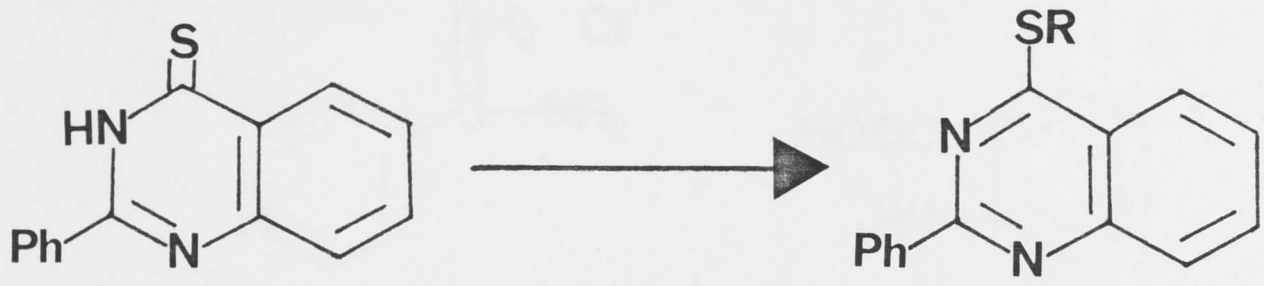
Aminolysis of 4-chloro-2-phenyl- (III.41)[15] and 2-chloro-4-phenyl-quinazoline (III.42)[16] with 2-dimethylaminoethylamine gave the quinazolinamines (III.43)[17] and (III.44) (Scheme III-11). S-Alkylation of 2-phenylquinazoline-4(3H)-thione (III.45)[18] and the positional isomer (III.48)[19] gave the thioethers (III.46,47,49,50) (Scheme III-12). Fusion of the amidine (III.13)[9] with anthranilic acid gave the quinazolin-4-one (III.51).[20] This was converted successively into the thione (III.52) and the thioether (III.53) (Scheme III-13) by thiation and alkylation.



	R^1	R^2
(III.41)	Ph	Cl
(III.42)	Cl	Ph

	R^1	R^2
(III.43)	Ph	$NHCH_2CH_2NMe_2$
(III.44)	$NHCH_2CH_2NMe_2$	Ph

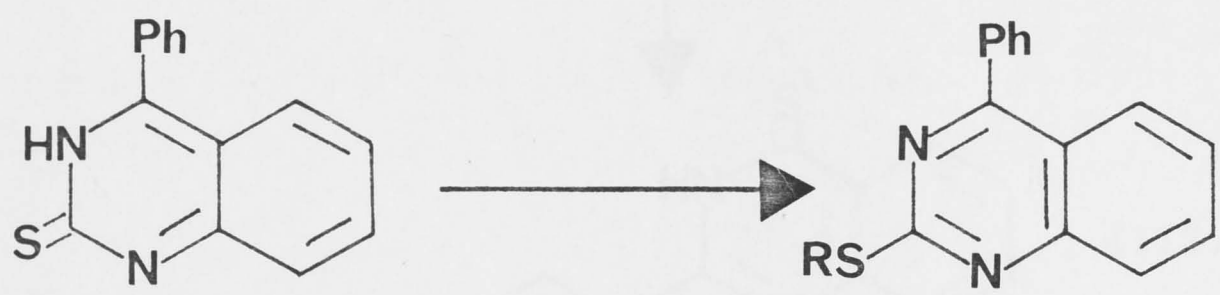
(Scheme III-11)



(III.45)

(III.46 ; R = $CH_2CH_2NMe_2$)

(III.47 ; R = $CH_2CH_2CH_2NMe_2$)

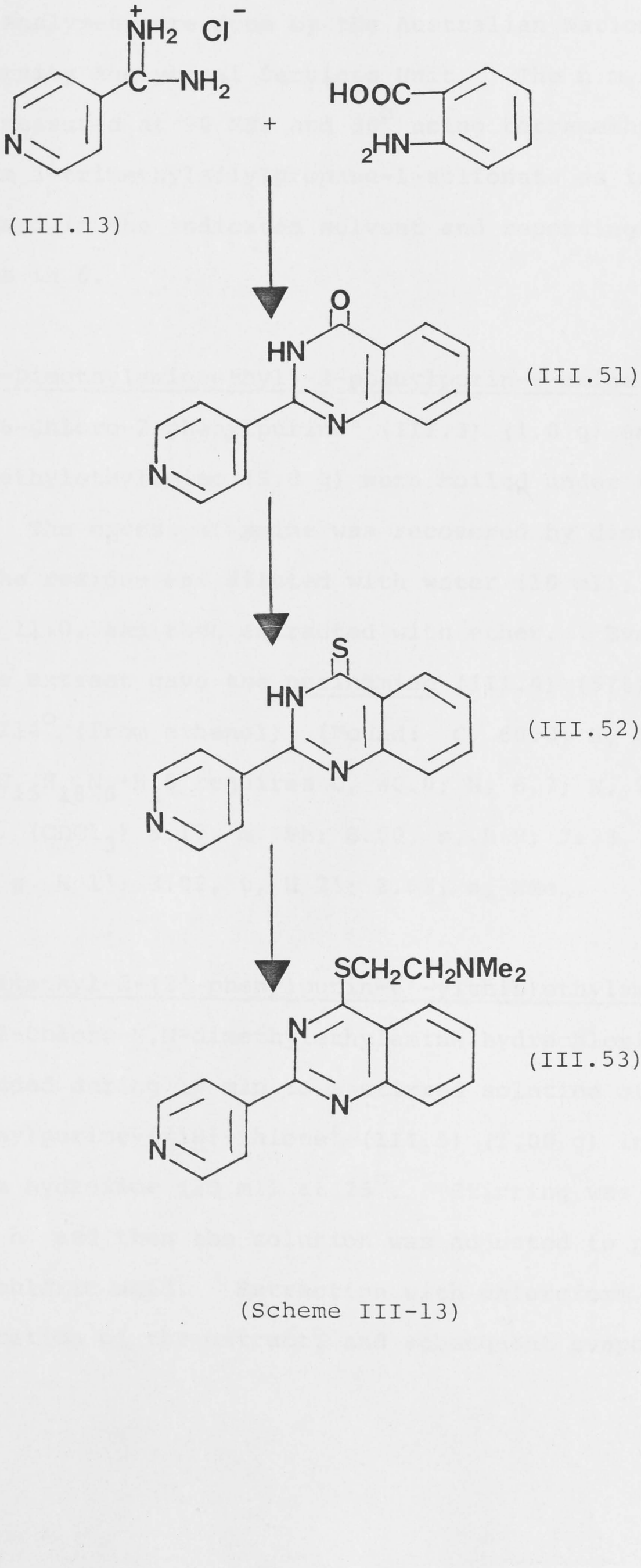


(III.48)

(III.49 ; R = $CH_2CH_2NMe_2$)

(III.50 ; R = $CH_2CH_2CH_2NMe_2$)

(Scheme III-12)



(III.13)

(III.51)

(III.52)

(III.53)

(Scheme III-13)

III-5 Experimental

Analyses were done by the Australian National University Analytical Services Unit. The n.m.r. spectra were measured at 90 MHz and 30° using tetramethylsilane or sodium 3-trimethylsilylpropane-1-sulfonate as internal standard in the indicated solvent and reporting chemical shifts in δ.

N-(2'-Dimethylaminoethyl)-2-phenylpurin-6-amine (III.4)

6-Chloro-2-phenylpurine[5] (III.3) (1.0 g) and 2-dimethylethylamine (5.0 g) were boiled under reflux for 2 h. The excess of amine was recovered by distillation and the residue was diluted with water (10 ml), adjusted to pH 11.0, and then extracted with ether. Evaporation of the extract gave the purinamine (III.4) (57%), m.p. 214° (from ethanol) (Found: C, 60.0; H, 6.3; N, 28.1 $C_{15}H_{18}N_6 \cdot H_2O$ requires C, 60.0; H, 6.7; N, 28.0%). N.m.r. ($CDCl_3$) 8.17, m, Ph; 8.00, s, H 8; 7.38, m, Ph; 3.97, g, H 1'; 3.02, t, H 2'; 2.63, s, NMe_2.

N,N-Dimethyl-2-(2'-phenylpurin-6'-ylthio)ethylamine (III.6)

2-Chloro-*N*,*N*-dimethylethylamine hydrochloride (0.80 g) was added during 10 min to a stirred solution of 2-phenylpurine-6(1*H*)-thione[6] (III.5) (1.00 g) in 2 *M* sodium hydroxide (20 ml) at 25°. Stirring was continued for 2 h. and then the solution was adjusted to pH 8 with hydrochloric acid. Extraction with chloroform, dehydration of the extract, and subsequent evaporation

gave the purinylthioethylamine (III.6) (73%), m.p. 163-165° (from ethyl acetate) (Found: C, 60.1; H, 5.6; N, 23.0. $C_{15}H_{17}N_5S$ requires C, 60.2; H, 5.7; N, 23.4%). N.m.r. ($CDCl_3$) 8.35, m, Ph; 8.05, s, H 8'; 7.41, m, Ph; 3.68, t, H 2; 2.90, t, H 1; 2.43, s, NMe_2.

6-Amino-2-phenylpurine-8(7H)-thione (III.8)

2-Phenylpyrimidine-4,5,6-triamine[7] (III.7) (1.0 g) and thiourea (1.0 g) were ground together and then fused at 220° for 1 h. A solution of the cooled mixture in 2 M sodium hydroxide was decolourized with carbon and then adjusted to pH 5-6 with hydrochloric acid to give the thione (III.8) (92%), m.p. 282° (from ethanol) (Found: C, 54.4; H, 3.7; N, 28.6. $C_{11}H_9N_5S$ requires C, 54.3; H, 3.7; N, 28.8%). N.m.r. (1 M NaOD) 8.00, m, Ph; 7.51, m, Ph.

8-(2'-Dimethylaminoethylthio)-2-phenylpurin-6-amine (III.9)

A solution of the above purinethione (III.8) (1.0 g) in 2 M sodium hydroxide (20 ml) was stirred while 2-chloro-N,N-dimethylethylammonium chloride (0.7 g) was added over 10 min. After stirring for a further 2 h, the mixture was extracted with chloroform. The dehydrated extract was evaporated to give the purinamine (III.9) (68%), m.p. 215° (from ethanol) (Found: C, 57.7; H, 5.8; N, 26.7. $C_{15}H_{18}N_6S$ requires C, 57.3; H, 5.8; N, 26.7%). N.m.r. [$(CD_3)_2SO$] 8.31, m, Ph; 7.43, m, Ph; 6.98, s, br, NH_2, 3.41, t, H 1'; 2.60, t, H 2', 2.21, s, NMe_2.

2-Methylthio-6-phenylpyrimidine-4,5-diamine (III.11)

4,5-Diamino-6-phenylpyrimidine-2(1H)-thione[8] (III.10) (1.0 g), 1 M sodium hydroxide (20 ml) and methyl iodide (1.0 ml) were stirred at 25° for 2 h. Filtration gave the methylthiopyrimidine (III.11) (69%), m.p. 211° (from ethanol) (Found: C, 56.7; H, 5.2; N, 24.0. $C_{11}H_{12}N_4S$ requires C, 56.9; H, 5.2; N, 24.1%).

2-Methylthio-6-phenylpurine (III.12)

The above methylthiopyrimidine (III.11) (0.50 g) and dimethoxymethyl acetate (10 ml) were boiled under reflux for 3 h. Evaporation in a vacuum gave the methylthiopurine (III.12) (63%), m.p. 258° (from ethanol) (Found: C, 59.6; H, 4.2; N, 23.0. $C_{12}H_{10}N_4S$ requires C, 59.5; H, 4.2; N, 23.1%). N.m.r. [$(CD_3)_2SO$] 8.79, m, Ph; 8.50, s, H 8; 2.64, s, Me.

5,6-Diamino-2-(pyridin-4'-yl)pyrimidin-4(3H)-one (III.15)

Pyridine-4-carboxamidinium chloride[9] (III.13) (3.16 g), ethyl 2-cyano-2-hydroxyiminoacetate (2.88 g) and ethanolic sodium ethoxide (sodium: 1.84 g; ethanol: 40 ml) were boiled under reflux for 20 h. Refrigeration gave crude 6-amino-5-nitroso-2-(pyridin-4'-yl)pyrimidine-4(3H)-one (III.14) as sodium salt, which was filtered off, washed with cold ethanol, and then stirred in water (80 ml) at 60° while sodium dithionite was added until the mixture became a clear solution and no further colour change occurred. After boiling for 10 min, the solution was

cooled to give the diaminopyrimidinone (III.15) (64%), m.p. >292° (dec.) (from methoxyethanol) (Found: C, 53.0; H, 4.4; N, 34.3. $C_9H_9N_5O$ requires C, 53.2; H, 4.5; N, 34.5%).

2-(Pyridin-4'-yl)purin-6(1H)-one (III.16)

The diaminopyrimidinone (III.15) (2.03 g), triethyl orthoformate (18.0 ml) and acetic anhydride (12.5 ml) were boiled under reflux for 15 min. The residue from evaporation in a vacuum was triturated with water and the solid was removed and washed with ether to give the purinone (III.16) (70%) m.p. >360° (from methoxyethanol) (Found: C, 56.5; H, 3.3; N, 33.0. $C_{10}H_7N_5O$ requires C, 56.3; H, 3.3; N, 32.9%). N.m.r. (NaOD/D_2O) 8.58, d, H 2', 6'; 8.03, d, H 3', 5'; 7.94, s, H 8.

N,N-Dimethyl-2-[2'-(pyridin-4"-yl)purin-6'-ylthio]-ethylamine (III.18)

The above purinone (III.16) (1.0 g), phosphorus pentasulfide (4.0 g) and pyridine (40 ml) were boiled under reflux for 4 h. The residue from removal of the solvent under reduced pressure was dissolved in 2 M sodium hydroxide (40 ml) and then reprecipitated by acidification with acetic acid. The crude pyridinylpurinethione (III.17) was redissolved in 1 M sodium hydroxide (40 ml) and 2-chloro-N,N-dimethylethylamine hydrochloride (1.0 g) was added. After stirring at 25° for 2 h, chloroform extraction and evaporation of the extract gave the product (III.18)

(52%), m.p. 182-183° (from ethyl acetate) (Found: C, 55.8; H, 5.2; N, 27.7. $C_{14}H_{16}N_6S$ requires C, 56.0; H, 5.4; N, 28.0%). N.m.r. ($CDCl_3$) 8.59, d, H 2", 6"; 8.18, d, H 3", 5"; 8.12, s, H 8'; 3.69, t, H 2; 2.97, t, H 1; 2.47, s, NMe_2.

N,N-Dimethyl-2-(8'-phenylpurin-6'-ylthio)ethylamine (III.20)

Alkylation of 8-phenylpurine-6(1H)-thione[10] (III.19) (0.5 g) with 2-chloro-N,N-dimethylethylamine hydrochloride (0.5 g), as for the isomer (III.6), gave the product (III.20) (71%), m.p. 232° (from ethanol) (Found: C, 60.5; H, 5.7; N, 22.9. $C_{15}H_{17}N_5S$ requires C, 60.2; H, 5.7; N, 23.4%). N.m.r. (1 M DCl) 8.92, s, H 2'; 7.83, m, Ph; 7.47, m, Ph; 3.77, t, H 2; 3.10, s, NMe_2; 2.80, t, H 1.

2-Chloro-8-phenylpurine (III.25)

(A) 2-Chloropyrimidine-4,5-diamine[11] (III.21) (1.40 g), benzaldehyde (1.20 g) and ethanol (30 ml) were boiled under reflux for 1 h and then cooled. Filtration of the suspension gave 5-benzylideneamino-2-chloropyrimidin-4-amine (III.22) (82%), m.p. 229° (from ethanol) (Found: C, 57.1; H, 3.8; Cl, 15.2; N, 23.7. $C_{11}H_9ClN_4$ requires C, 56.8; H, 3.9; Cl, 15.2; N, 24.1%).

The Schiff base (III.22) (1.0 g), N-bromosuccinimide (0.9 g) and chloroform (30 ml) were boiled under reflux for 90 min. The residue from evaporation was triturated with water to give the chloropurine (III.25) (75%), m.p. 285° (from ethanol) (Found: C, 56.7; H, 3.2;

N, 23.7. $C_{11}H_7ClN_4$ requires C, 57.3; H, 3.1; N, 24.1%). N.m.r. [$(CD_3)_2SO$] 8.94, s, H 6; 8.20, m, Ph; 7.66, m, Ph.

(B) 4,5-Diaminopyrimidin-2(1H)-one[12] (III.23) (1.2 g), benzoyl chloride (1.5 g) and 1 M sodium hydroxide were stirred vigorously for 30 min and then acidified to pH 5. Filtration gave N-(4-amino-1,2-dihydro-2-oxopyrimidin-5-yl)-benzamide (III.24) (87%), m.p. 321° (dec.) (from methoxyethanol) (Found: C, 57.0; H, 4.5; N, 24.1. $C_{11}H_{10}N_4O_2$ requires C, 57.4; H, 4.4; N, 24.3%). N.m.r. [$(CD_3)_2SO$] 9.49, s, H 6; 7.95, m, Ph; 7.55, m, Ph; 7.00, s, br, NH.

The amide (III.24) (0.5 g) and P-dichloro-P-phenylphosphine oxide (10.0 g) were heated under reflux for 6 h. The cooled mixture was added to ice water and allowed to stand in the refrigerator for 12 h. The solid (76%) was proved to be identical with the product (III.25) in (A) above.

8-Phenylpurine-2(1H)-thione (III.26)

The above chloropurine (III.25) (0.80 g), thiourea (0.30 g) and ethanol (20 ml) were boiled under reflux for 1 h. After cooling the solution the thione (III.26) (79%) was filtered off. It had m.p. 303° (from ethanol) (cf[13] >300°; 5%) (Found: C, 57.5; H, 3.2; N, 24.4. Calc. for $C_{11}H_8N_4S$: C, 57.9; H, 3.5; N, 24.5%). N.m.r. [$(CD_3)_2SO$] 9.01, s, H 6; 8.21, m, Ph; 7.62, m, Ph.

6-(2'-Dimethylaminoethyl)amino-5-nitro-2-phenylpyrimidine-4-amine (III.28)

6-Chloro-5-nitro-2-phenylpyrimidin-4-amine[14] (III.27) (2.0 g) and 2-dimethylaminoethylamine (6.0 g) were boiled under reflux for 20 min. The cooled mixture was diluted with water and filtration gave the nitropyrimidine (III.28) (8%), m.p. 168° (from ethanol) (Found: C, 53.0; H, 5.8; N, 26.7. $C_{14}H_{18}N_6O_2 \cdot 0.75\ H_2O$ requires C, 53.3; H, 6.2; N, 26.6%). N.m.r. ($CDCl_3$) 8.38, m, Ph; 7.48, m, Ph; 3.84, q, H'; 2.62, t, H 2'; 2.32, s, NMe_2; 1.58, s, NH.

6-(2'-Dimethylaminoethyl)amino-2-phenylpyrimidine-4,5-diamine Dihydrochloride (III.29)

The above nitropyrimidine (III.28) (2.0 g) was stirred in water (40 ml) at 80° while sodium dithionite (10.0 g) was added during 5 min. The mixture was allowed to cool with stirring and then adjusted to pH 10. The suspension was extracted with ether and evaporation of the extract gave the crude base (64%) which was characterized as the 4,5-diaminopyrimidine dihydrochloride (III.29) m.p. 266° (from ethanol) (Found: C, 48.5; H, 6.6; N, 24.1. $C_{14}H_{20}N_6 \cdot 2HCl$ requires C, 48.7; H, 6.4; N, 24.3%). N.m.r. (D_2O) 7.97, m, Ph; 7.69, m, Ph; 4.06, q, H 1'; 3.50, t, H 2'; 2.98, s, NMe_2.

N-(2'-Dimethylaminoethyl)-2-phenylpteridin-4-amine (III.30) and its 6,7-Dimethyl Derivative (III.31)

The above crude base (III.29) (0.5 g), 40% aqueous glyoxal (0.5 g) [or diacetyl (0.3 g)], and ethanol (10 ml) were heated under reflux for 1 h. The residue from evaporation in a vacuum was triturated with water and filtration gave, respectively, the pteridineamine (III.30) (52%), m.p. 173° (from acetone) (Found: C, 65.2; H, 6.2; N, 28.4. $C_{16}H_{18}N_6$ requires C, 65.3; H, 6.2; N, 28.5%). [N.m.r. ($CDCl_3$) 8.97, d, H 6; 8.78, d H 7; 8.60, m, Ph; 7.53, m, Ph; 3.86, q, H 1'; 2.70, t, H 2'; 2.36, s, NMe_2] or the dimethylpteridinamine (III.31) (61%), m.p. 157° (from acetone) (Found: C, 66.0; H, 6.91; N, 26.0. $C_{18}H_{22}N_6$ requires C, 67.0; H, 6.9; N, 26.1%) [N.m.r. ($CDCl_3$) 8.67, m, Ph; 7.46, m, Ph; 3.86, q, H 1'; 2.73, s, 6-Me; 2.67, s, 7-Me; 2.67, t, H 2'; 2.35, s, NMe_2].

4-Methylthio-2-phenylpteridine (III.35) and 6,7-Dimethyl-4-methylthio-2-phenylpteridine (III.36)

5,6-Diamino-2-phenylpyrimidine-4(3H)-thione[14] (III.32) (1.0 g) 40% aqueous glyoxal (1.0 g) and water (20 ml) were heated under reflux for 1 h. Cooling and filtration gave 2-phenylpteridine-4(3H)-thione (III.33) (54%), m.p. >225° (dec) (from ethanol) (Found: C, 59.9; H, 3.5; N, 23.3. $C_{12}H_8N_4S$ requires C, 60.0; H, 3.4; N, 23.3%). N.m.r. [$(CD_3)_2SO$] 9.07, d, H 6; 8.87, d, H 7; 8.19, m, Ph; 7.61, m, Ph. The same substrate (1.0 g), diacetyl (0.5 g) and 95% ethanol (20 ml) were heated under reflux for 1 h.

The residue from evaporation was diluted with a little water to give 6,7-dimethyl-2-phenyl-4(3H)-thione (III.34) (58%), m.p. >210° (dec.) (from ethanol) (Found: C, 62.6; H, 4.4; S, 11.7. $C_{14}H_{12}N_4S$ requires C, 62.7; H, 4.5; S, 11.9%). N.m.r. [$(CD_3)_2SO$] 8.17, m, Ph; 7.59, m, Ph; 2.66, s, 6,7-Me_2.

Each thione (0.5 g), methyl iodide (1.0 ml) and 1 M sodium hydroxide (20 ml) were shaken at 25° for 2 h. Refrigeration gave, respectively, the thioether (III.35) (92%) m.p. 189° (from ethanol) (Found: C, 61.6; H, 3.9; N, 22.0. $C_{13}H_{10}N_4S$ requires C, 61.4; H, 4.0; N, 22.0%). [N.m.r. in $(CD_3)_2SO$: 9.29, d, H 6; 8.98, d, H 7; 8.64, m, Ph; 7.62, m, Ph; 2.81, s, Me] and its 6,7-dimethyl derivative (III.36) (97%), m.p. 163° (from ethanol) (Found: C, 61.2; H, 4.8; N, 19.0. $C_{15}H_{14}N_4S.0.5\ H_2O$ requires C, 61.8; H, 5.2; N, 19.2%). N.m.r. [$(CD_3)_2SO$] 8.59, m, Ph; 7.59, m, Ph; 2.76, s, SMe; 2.75, s, 6-Me; 2.71, s, 7-Me.

2-Chloro-6,7-dimethyl-4-phenylpteridine (III.38)

2-Chloro-6-phenylpyrimidine-4,5-diamine[11] (III.37) (0.5 g), diacetyl (0.2 g) and 50% aqueous ethanol (20 ml) were heated under reflux for 2 h and then refrigerated to give the chloropteridine (III.38) (57%), m.p. 185-186° (from ethanol) (Found: C, 60.5; H, 3.9; N, 19.5. $C_{14}H_{11}ClN_4.\ 0.5\ H_2O$ requires C, 60.1; H, 4.3; N, 20.0%). N.m.r. [$(CD_3)_2SO$] 8.33, m, Ph; 7.66, m, Ph; 2.80, s, 6-Me; 2.75, s, 7-Me.

2-Methylthio-4-phenylpteridine (III.39) and 6,7-Dimethyl-2-methylthio-4-phenylpteridine (III.40)

2-Methylthio-6-phenylpyrimidine-4,5-diamine (III.11) (0.6 g), ethanol (20 ml) and 40% aqueous glyoxal (0.6 g) or diacetyl (0.2 g) were heated under reflux for 1 h and then refrigerated to give, respectively, the pteridine (III.39) (68%), m.p. 176° (from ethanol) (Found: C, 61.2; H, 3.9; N, 21.9 $C_{13}H_{10}N_4S$ requires C, 61.4; H, 4.0; N, 22.0%) [N.m.r. in $(CD_3)_2SO$: 9.20, d, H 6; 9.02, d, H 7; 8.24, m, Ph; 7.6, m, Ph; 2.71, s, SMe] and the dimethylpteridine (III.40) (73%), m.p. 169° (from ethanol) (Found: C, 63.5; H, 5.0; N, 19.8 $C_{15}H_{14}N_4S$ requires C, 63.8; H, 5.0; N, 19.8%). [N.m.r. in $(CD_3)_2SO$: 8.28, m, Ph; 7.59, m, Ph; 2.75, s, SMe; 2.69, s, 6-Me, 2.67, s, 7-Me].

N-(2'-Dimethylaminoethyl)-2-phenylquinazolin-4-amine (III.43)

4-Chloro-2-phenylquinazoline[15] (III.41) (1.0 g) and 2-dimethylaminoethylamine (5 g) were boiled under reflux for 2 h. The excess amine was removed by distillation and the residue was diluted with water (8 ml) and adjusted to pH 10. The residue from evaporating an ether extract was dissolved in ethanol (10 ml) and to this was added ethanolic 5 M hydrogen chloride (4.0 ml). After warming momentarily to attain homogeneity, refrigeration gave the product (III.43) as dihydrochloride (89%), m.p. 273° (from ethanol) (Found: C, 59.1; H, 6.5; N, 15.3.

$C_{18}H_{20}N_4.2HCl$ requires C, 59.2; H, 6.1; N, 15.3%).
A dihydrochloride with the same melting point has been described previously[17] as a sesquihydrate.

N-(2'-Dimethylaminoethyl)-4-phenylquinazolin-2-amine (III.44)

Similar treatment of 2-chloro-4-phenylquinazoline[16] (III.42) gave the product (III.44) as hydrochloride (91%), m.p. 234-236° (Found: C, 61.0; H, 6.2; N, 15.8. $C_{18}H_{20}N_4 \cdot 1.7\ HCl$ requires C, 61.1; H, 6.3; N, 15.8%; this composition was maintained during several recrystallizations from ethanol).

N,N-Dimethyl-2-(2'-phenylquinazolin-4'-ylthio)ethylamine (III.46) and N,N-Dimethyl-3-(2'-phenylquinazolin-4'ylthio)-propylamine (III.47)

2-Phenylquinazoline-4(3H)-thione[18] (III.45) (1.0 g), 2-chloro-N,N-dimethylethylamine hydrochloride (0.8 g) and 2 M sodium hydroxide (20 ml) were stirred at 25° for 2 h. The solution was adjusted to pH 8 and extracted with ether. After dehydration of the extract, 5 M ethanolic hydrogen chloride (4.0 ml) was added and refrigeration gave the ethylamine (III.46) as hydrochloride (88%), m.p. 218° (from ethanol) (Found: C, 62.1; H, 5.8; N, 11.7. $C_{18}H_{19}N_3S.HCl$ requires C, 62.5; H, 5.8; N, 12.1%).

The use of 3-chloro-N,N-dimethylpropylamine hydrochloride in the above preparation afforded the homologous propylamine (III.47), as hydrochloride (67%), m.p. 126-128° (from ethanol) (Found: C, 63.4; H, 6.3; N, 11.8. $C_{19}H_{21}N_3S$ requires C, 63.4; H, 6.2; N, 11.7%).

N,N-Dimethyl-2-(4'-phenylquinazolin-2'-ylthio)ethylamine (III.49) and N,N-Dimethyl-3-(4'-phenylquinazolin-2'-ylthio)-propylamine (III.50)

S-Alkylation of 4-phenylquinazoline-2(1H)-thione[19] (III.48), as for the above isomers (III.46) and (III.47), gave the ethylamine (III.49) as hydrated hydrochloride (91%), m.p. 208° (from ethanol) (Found: C, 61.5; H, 5.8; N, 12.0. $C_{18}H_{19}N_3S \cdot 0.25\ H_2O \cdot HCl$ requires C, 61.7; H, 5.9; N, 12.0%). and the propylamine (III.50) as hydrochloride (54%), m.p. 173-174° (from ethanol) (Found: C, 63.2; H, 6.1; N, 11.4. $C_{19}H_{21}N_3S \cdot HCl$ requires C, 63.4; H, 6.2; N, 11.7%).

N,N-Dimethyl-2-[2'-(pyridin-4'-yl)quinazolin-4'-ylthio]-ethylamine (III.53)

Pyridine-4-carboxamidinium chloride[9], (III.13) (3.0 g) and anthranilic acid (1.0 g) were fused together at 180-190° for 30 min. The cooled residue was triturated with water and filtered to give 2-(pyridin-4'-yl)quinazolin-4-(3H)-one (III.51) (76%), m.p. 283° (from ethanol) (Found: C, 69.5; H, 4.0; N, 18.8. Calc. for $C_{13}H_9N_3O$: C, 69.8; H, 4.1; N, 18.8%) (cf. 290-294° for the same material made by a less convenient route[17]). The quinazolinone (1.0 g), phosphorus pentasulfide (1.0 g) and pyridine (40 ml) were warmed slowly to boiling and then kept under reflux for 1 h. The cooled mixture was added to ice water (150 ml) and allowed to stand at 5° for 24 h. The crude thione (III.52) (cf.[17,20]) was dissolved in 1 M sodium hydroxide (40 ml) and stirred for 2 h with 2-chloro-N,N-dimethylethylamine hydrochloride. Ether extraction and

evaporation of the extract gave the required ethylamine (III.53) (40%), m.p. 92-93° (from light petroleum) (Found: C, 65.5; H, 5.9; N, 18.0. $C_{17}H_{18}N_4S$ requires C, 65.8; H, 5.8; N, 18.0%). N.m.r. ($CDCl_3$) 8.80, d, H 2", 6"; 8.43, d, H 3", 5"; 7.84, m, H 5'-8'; 3.66, t, H 1; 2.80, t, H 2; 2.38, s, NMe_2.

REFERENCES

1. D. J. Brown and W. B. Cowden, Aust. J. Chem., 35, 1203 (1982);
   D. J. Brown and W. B. Cowden, Aust. J. Chem., 36, 1469 (1983);
   D. J. Brown, W. B. Cowden, S.-B. Lan and K. Mori, Aust. J. Chem., 37, 155 (1984).

2. T. E. Allen, D. J. Brown, W. B. Cowden, G. W. Grigg, N. K. Hart, J. A. Lamberton, and A. Lane, J. Antibiot., 37, 376 (1982).

3. D. J. Brown and G. W. Grigg, Med. Res. Rev., 2, 193 (1982).

4. A. N. Aliano, T. E. Allen, D. J. Brown, W. B. Cowden, G. W. Grigg, D. Kavulak, and S.-B. Lan, Aust. J. Chem., 37, 2385 (1984).

5. W. Traube and L. Herrmann, Ber. Dtsch. Chem. Ges., 37, 2267 (1904).

6. F. Bergmann, A. Kalmas, H. Ungar-Waron, and H. Kwietny-Govrin, J. Chem. Soc., 3729 (1963).

7. R. M. Evans, P. G. Jones, P. J. Palmer, and F. P. Stephens, J. Chem. Soc., 4106 (1956).

8. J. Clark and P. N. T. Murdoch, J. Chem. Soc.(C)., 1883 (1969).

9. B. Singh and G. Y. Lesher, J. Heterocycl. Chem., 14, 1413 (1977).

10. S. C. J. Fu, E. Chinoporos, and H. Terzian, J. Org. Chem., 30, 1916 (1965).

11. A. Nagel, H. C. van der Plas, and A. van Veldhuizen, Recl. Trav. Chim. Pays-Bas, 94, 45 (1975).

12. C. O. Johns, Am. Chem. J., 45, 79 (1911).

13. R. J. Badger, D. J. Brown, and J. H. Lister, J. Chem. Soc., Perkin Trans. 1, 1906 (1973).

14. J. Clark, P. N. T. Murdoch, and D. L. Roberts, J. Chem. Soc., (C), 1408 (1969).

15. E. W. Endicott, M. L. Mercury, and M. L. Sherrill, J. Am. Chem. Soc., 68, 1299 (1946).

16. K. Schofield, J. Chem. Soc., 1927 (1952).

17. H. M. Blatter, U.S. Pat. 3, 340, 260 (1967); Chem. Abstr., 69, 19205 (1968).

18. D. Libermann and A. Rouaix, Bull. Soc. Chim. Fr., 1793 (1959).

19. A. V. Bogatskii, S. A. Andronati, Z. I. Zhilina, and N. I. Danilina, Zh. Org. Khim., 13, 1773 (1977); Chem. Abstr., 88, 6829r (1978).

20. I. Y. Postovskii, N. N. Vereschagina, and S. L. Mertsalov, Khim. Geterotskil. Soedin. Akad. Nauk. Latv. SSR., 130 (1966); Chem. Abstr., 65, 711 (1966).

CHAPTER IV

BIOLOGICAL ACTIVITIES

IV-1 Biological Results

The pyrimidinylpurine, phenylpurine, pyrimidinylpteridine, phenylpteridine, and phenylquinazoline derivatives, described in CHAPTER II and III and listed in Tables 1-4, were evaluated* as amplifiers of phleomycin-G against an *in vitro* culture of *Escherichia coli*. Caffeine was taken as a standard, with 1-star activity at 2mM or 0.5mM concentration.

Table 1 lists the activities for the 2-(pyrimidin-4'-yl)purines (II.20-22,24,25,27). Among these compounds, (II.21) showed only moderate activity (3-star), (II.22,24,27) showed mediocre activity, and (II.20,25) were too poorly soluble for effective testing.

Table 2 shows activities for some phenylpurines (III.4,6,9,12,20), and one 2-(pyridin-4'-yl)purine (III.18). The best of these compounds was (III.6) with 'high activity' (4-star); its analogues (III.4,9,20) showed only 2-star activity, and the 2-pyridin-4'-yl analogue (III.18) could not be evaluated in the standard test system because of its intrinsic antibacterial activity.

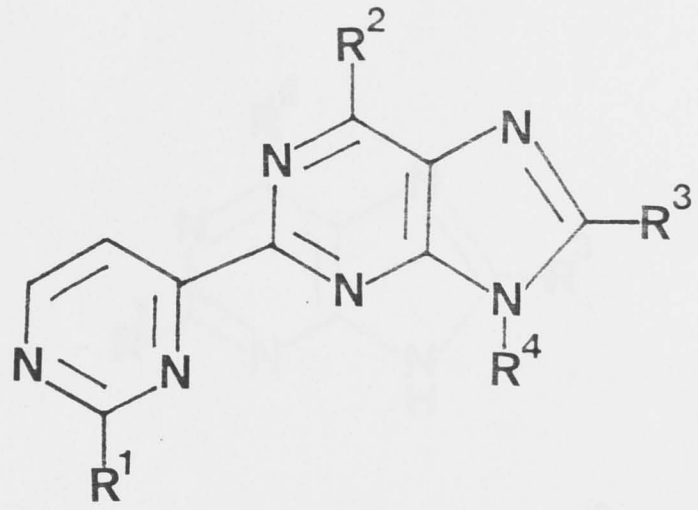
---

* Such assays were kindly done by Mrs D. Kavulak, CSIRO Molecular & Cellular Biology Unit, using a method already described.[1]

In Table 3 are shown activities for a 2-(pyrimidin-4'-yl)pteridine (II.33) and some analogous phenylpteridines (III.30,31,35,36,39,40). Of these, only (III.31) showed moderate 3-star activity; (III.30,36) showed 1-star activity; the methylthio analogues (III.35,39,40) were too poorly soluble for testing; and the pyrimidinylpteridine (II.33) could not be evaluated because of antibacterial activity.

Table 4 shows the results for some phenylquinazolines (III.43,44,46,47,49,50) and for the 2-pyridin-4'-yl analogue (III.53). Although (III.46) showed high 4-star activity, its analogues (III.44,49,50) showed only low to moderate (2-star) activities, (III.43) showed minimal 1-star activity, and the 2-pyridin-4'-yl analogue (III.53) could not be evaluated on account of its antibacterial activity.

Table 1

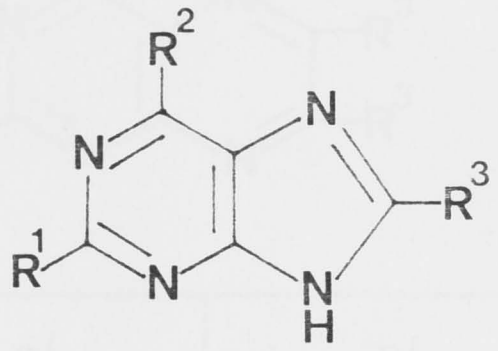


Compound	R^1	R^2	R^3	R^4	Activity†
(II.20)	NMe_2	SMe	H	H	-A
(II.21)	NMe_2	$SCH_2CH_2NMe_2$	H	H	***
(II.22)	OMe	$NHCH_2CH_2NMe_2$	H	H	*
(II.24)	NMe_2	NH_2	$SCH_2CH_2NMe_2$	H	*
(II.25)	NMe_2	NHAc	$SCH_2CH_2NMe_2$	Ac	-A
(II.27)	OMe	NH_2	$SCH_2CH_2NMe_2$	H	**

† Measured at 2mM
for definitions of activity
see D. J. Brown et al. (1981)[1]

A Solubility precluded measurement

Table 2



Compound	R^1	R^2	R^3	Activity†
(III.4)	Ph	$NHCH_2CH_2NMe_2$	H	**[A]
(III.6)	Ph	$SCH_2CH_2NMe_2$	H	****
(III.9)	Ph	NH_2	$SCH_2CH_2NMe_2$	**[B]
(III.12)	SMe	Ph	H	o[B]
(III.18)	Pyridin-4-yl	$SCH_2CH_2NMe_2$	H	-[C]
(III.20)	H	$SCH_2CH_2NMe_2$	Ph	**

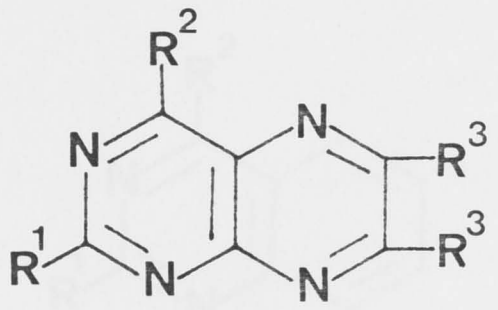
† Measured at 0.5mM

A At 2mM

B At < 0.5mM (saturated) against caffeine at 0.5mM

C Intrinsic antibacterial activity precluded measurement

Table 3



Compound	R^1	R^2	R^3	Activity†
(II.33)	2-methoxy-pyrimidin-4-yl	$NHCH_2CH_2NMe_2$	H	-[A,C]
(III.30)	Ph	$NHCH_2CH_2NMe_2$	H	*
(III.31)	Ph	$NHCH_2CH_2NMe_2$	Me	***
(III.35)	Ph	SMe	H	0[B]
(III.36)	Ph	SMe	Me	*[A]
(III.39)	SMe	Ph	H	0[B]
(III.40)	SMe	Ph	Me	0[B]

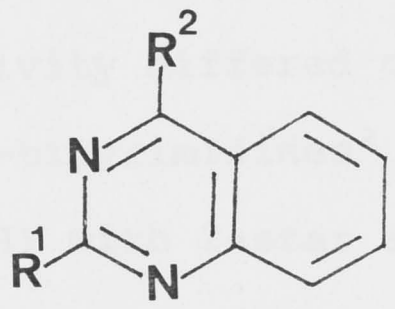
† Measured at 0.5mM

A At 2mM

B At < 0.5mM (saturated) against caffeine at 0.5mM

C Intrinsic antibacterial activity precluded measurement

Table 4



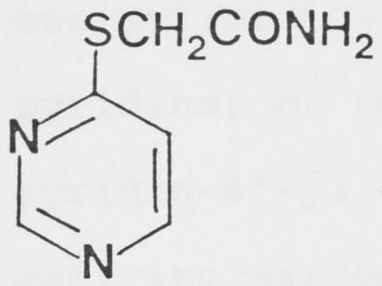
Compound	R^1	R^2	Activity†
(III.43)	Ph	$NHCH_2CH_2NMe_2$	*
(III.44)	$NHCH_2CH_2NMe_2$	Ph	**
(III.46)	Ph	$SCH_2CH_2NMe_2$	****
(III.47)	Ph	$SCH_2CH_2CH_2NMe_2$	-A
(III.49)	$SCH_2CH_2NMe_2$	Ph	**
(III.50)	$SCH_2CH_2CH_2NMe_2$	Ph	**
(III.53)	pyridin-4-yl	$SCH_2CH_2NMe_2$	-A

† Measured at 0.5mM

A Intrinsic antibacterial activity precluded measurement

IV-2 Discussion

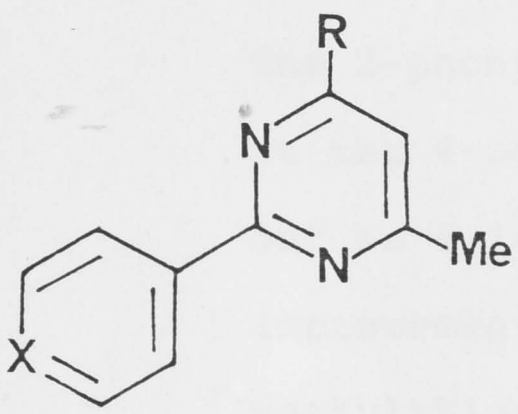
The annelation (fusion) of a imidazole ring onto a 2,4'-bipyrimidine bearing a suitable side chain did not improve activity. Thus, the 2-(pyrimidin-4'-yl)purine (II.21) with 3-star activity and its analogue (II.22) with 1-star activity differed only slightly from comparable 2,4'-bipyrimidines[2] such as (IV.2) with 3-star and (IV.3) with 2-star activity (see Scheme IV-1). On the other hand, the addition of an (unfused) pyrimidine ring to a purine improved activity, so that (II.21) with 3-star proved much more active than the comparable purine (IV.5) with 1-star activity.[2] Relocation of the basic side chain from the 6- to the 8—position in the pyrimidinylpurines had a mildly deleterious effect. Thus, the 8-thioether (II.24) showed 1-star activity compared to the 3-star activity of the analogous 6-thioether (II.21); another 8-thioether (II.27) showed a marginal improvement from 1- to 2-star activity when compared with its 6-analogue (II.22), but this was probably on account of the additional change from a nitrogen- to a more desirable sulfur-linkage of the side chain.[1] The acetyl derivative (II.25) was very poorly soluble. The effect of similarly annelating a pyrazine ring onto a 2,4'-bipyrimidine system remains unknown because the 2-(pyrimidin-4'-yl)pteridine (II.33), so formed, proved to have intrinsic antibacterial activity and hence could not be tested effectively in the only screen available.[1]



(IV.1)

(IV.2; R=$NHCH_2CH_2NMe_2$)

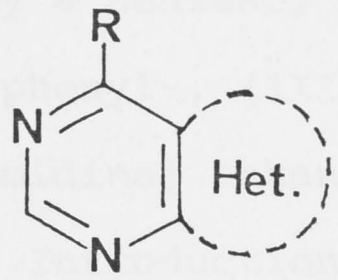
(IV.3; R=$SCH_2CH_2NMe_2$)



(III.1a; X=N, R=$SCH_2CH_2NMe_2$)

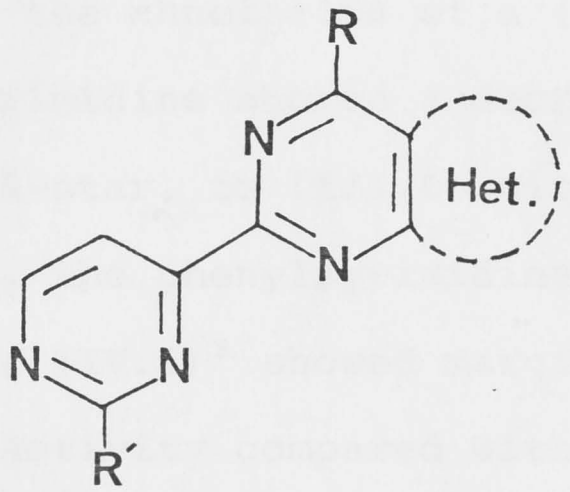
(III.2 ; X=CH, R=$SCH_2CH_2NMe_2$)

(IV.4 ; X=CH, R=$NHCH_2CH_2NMe_2$)

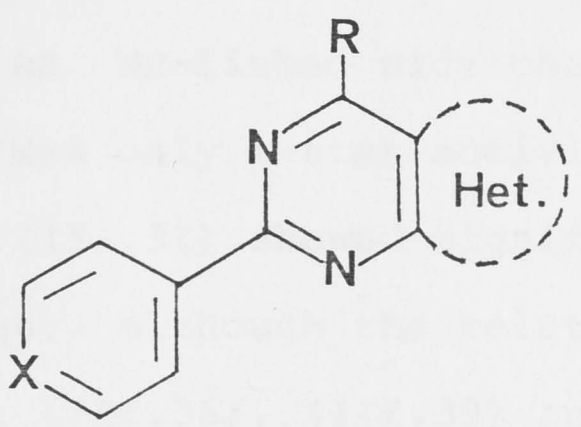


(IV.5; R=$SCH_2CH_2NMe_2$, Het=imidazole)

(IV.6; R=SCH_2CONH_2, Het=benzene)



(II. analogues)



(III. analogues)

Scheme IV-1

It was observed recently that the replacement of one pyrimidine ring in a bipyrimidine by a benzene, pyridine, or thiophene ring [to give a phenyl-, (III.2), pyridin-4'-yl (III.1a), or thienyl-pyrimidine] enhanced activity markedly[3-5](see CHAPTER III-1, Introduction). The effect of similarly adding an (unfused) benzene ring to a purine (to give a phenylpurine) showed an improvement from (II.21) with 3-star, to (III.6) with 4-star activity (Table 2); on the other hand, the annelation of a (fused) imidazole ring onto a phenylpyrimidine showed a decrease in activity from (III.2) with 5-star, to (III.6) with 4-star activity. In contrast, the phenylpyrimidine bearing an NH-linked side chain (IV.4)[3] showed marginal improvement from 1- to 2-star activity compared with (III.4). The pyridin-4'-yl analogue (III.18) could not be evaluated because of its intrinsic antibacterial activity, and the phenylpurines (III.20), (III.4), and (III.9) showed only 2-star activities. The methylthio analogue (III.12) proved virtually inactive (Table 2). The 2-phenylpteridine bearing an NH-linked side chain at the 4-position (III.30) showed only 1-star activity but is 6,7-dimethyl homologue (III.31) showed significant improvement to the 3-star range; although the related methylthiopteridines (III.35), (III.36), (III.39) and (III.40) showed minimal activities, it is clear that the 4-dimethylaminoethylthio analogue of the active amplifier (III.31) should be prepared for evaluation. The annelation of a (fused) pyrazine ring onto phenyl-pyrimidine bearing an NH-linked side chain improved

activity: although (III.30) as well as (IV.4) showed only 1-star activity, the 6,7-dimethyl homologue (III.31) showed marked improvement to 3-star activity (cf. the effect of added C-methyl groups on the activity of alkylthiopurines[6]).

The best quinazoline derivative was that with a 2-phenyl group and a sulfur-linked side chain in the 4-position (III.46) (4-star activity: see Table 4); the annelation of a (fused) benzene ring onto the phenylpyrimidine (III.2) was accompanied by a decrease in activity from 5- to 4-star in (III.46), but the addition of an (unfused) benzene ring onto the quinazoline (IV.6)[7,8] improved activity from 3- to 4-star. The isomer (III.49) and its homologue (III.50) showed only 2-star activities, while the NH-linked analogues (III.43) and (III.44) showed 1- and 2-star activity, respectively. The related compound (III.47) and the 2-pyridin-4'-yl analogue (III.53) of the prime amplifier (III.46) exhibited sufficient antibacterial activity to preclude testing. This was disappointing because (III.47) was expected to show high activity, being a fused analogue of (III.1a) with 5-star activity. The 2-(pyridin-4'-yl)purine (III.18) likewise showed sufficient antibacterial activity to preclude testing.

REFERENCES

1. D. J. Brown, B. B. Buttler, W. B. Cowden, G. W. Grigg, D. Kavulak, and D. M. Podger, Aust. J. Chem., 34, 2423 (1981).

2. G. B. Barlin, Aust. J. Chem., 35, 2299 (1982)

3. D. J. Brown, W. B. Cowden, S. B. Lan, and K. Mori, Aust. J. Chem., 37, 155 (1984).

4. D. J. Brown and W. B. Cowden, Aust. J. Chem., 35, 1203 (1982).

5. D. J. Brown, W. B. Cowden, and L. Strekowski, Aust. J. Chem., 35, 1209 (1982).

6. D. J. Brown, R. L. Jones, A. M. Angyal, and G. W. Grigg, J. Chem. Soc., Perkin Trans 1, 1819 (1972).

7. D. J. Brown, G. W. Grigg, Y. Iwai, K. N. McAndrew, T. Nagamatsu, and R. van Heeswyck, Aust. J. Chem., 32, 2713 (1979).

8. D. J. Brown, L. Danckwerts, G. W. Grigg, and Y. Iwai, Aust. J. Chem., 32, 453 (1979).

INDEX TO COMPOUNDS*

---

*New compounds in italic type.